HETEROCYCLES, Vol. 106, No. 3, 2023, pp. 423 - 438. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2022, Accepted, 28th September, 2022, Published online, 7th October, 2022
DOI: 10.3987/REV-22-993

HYDROXYCHLOROQUINE: CHEMISTRY AND MEDICINAL APPLICATIONS

Nidhi Yadav,[a,b] Yogesh Kumar Tyagi,[a]* and Ram Singh[b]*

[a]USBAS, Guru Gobind Singh Indraprastha University, Delhi - 110078, India
[b]Department of Applied Chemistry, Delhi Technological University, Delhi - 110042, India, ramsingh@dtu.ac.in

Abstract – Hydroxychloroquine (HCQ) is a molecule from the 4-aminoquinoline family which is utilized for the treatment of many diseases. This is one of the essential drugs, as per WHO. HCQ has been an anti-malarial drug and is also used for the treatment of autoimmune and rheumatic diseases. This molecule is repurposed for many types of diseases, either alone or in combination with other drugs. This review article discusses its synthetic methodologies and approved applications along with repurposed studies. This article covers HCQ applications in anti-cancer activity, anti-rheumatic activity, epigenetic activity, systemic lupus erythematosus, and COVID-19.

1. INTRODUCTION

Hydroxychloroquine (HCQ) (2-[[4-[(7-chloroquinolin-4-yl)amino]pentyl]ethylamino]ethanol) was licensed for medicinal use by the FDA in 1955.[1] It belongs to the 4-aminoquinoline family and has an aromatic structure that is flat. This is a biologically active molecule and has been successfully utilized to treat malaria. This molecule has also been used for prophylaxis and connective tissue disease.[2,3] Because of the presence of a basic side chain, it is a weak base that contributes to drug accumulation in lysosomal intracellular compartments. This is necessary for the activity and facilitation of interaction with nucleic acids. HCQ has *R* and *S* isomers, i.e., it exists as enantiomers (Figure 1). The presence of (*S*)-(+)-hydroxychloroquine concentration is low in blood than the counter isomer (*R*)-(-)-hydroxychloroquine.[1] This also confirms the role of stereoselective processes in the drug's metabolism and/or deposition. There have been several studies on its synthesis and applications. This review article discusses its synthetic methodologies, approved applications, and repurposed studies.

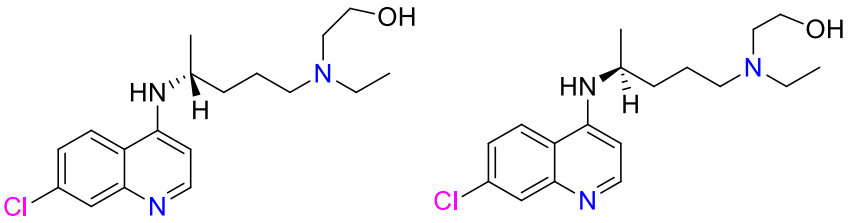


Figure 1. Structures of hydroxychloroquine isomers

2. SYNTHESIS OF HYDROXYCHLOROQUINE

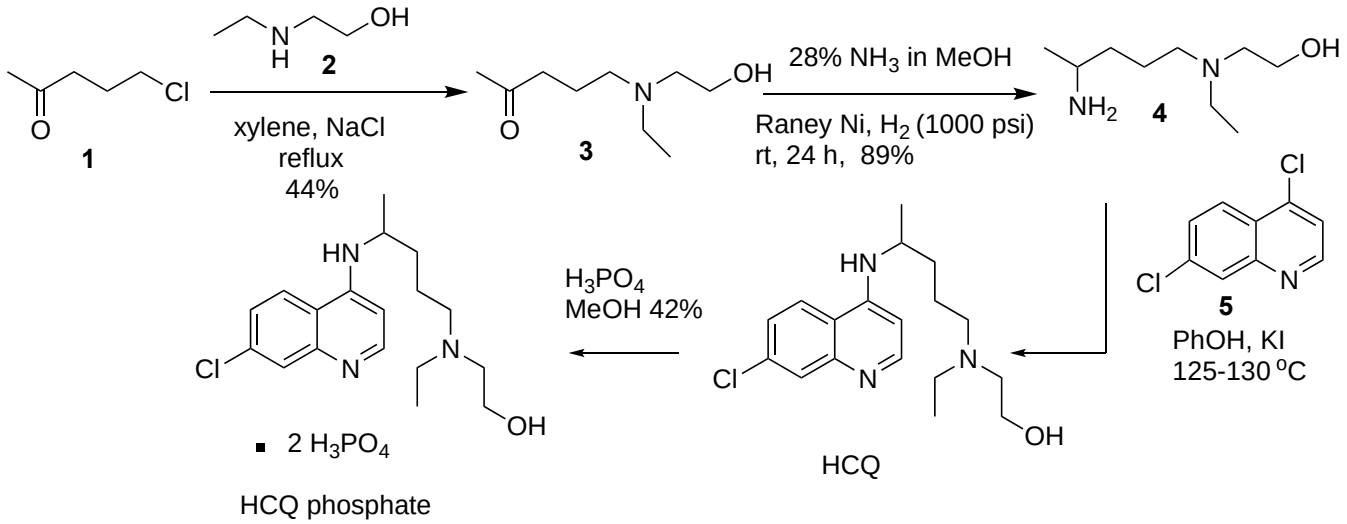
According to a US Patent granted in 1951, the synthesis of HCQ was done in three steps.[4,5] The alkylation of 1-chloro-4-pentanone (**1**) was done in the first step, which takes place in xylene under refluxing conditions for 3 h with *N*-ethyl-*N*-hydroxyethylamine (**2**). The obtained tertiary amine **3** was purified and isolated in 44% yield through vacuum distillation. The second step involved the reductive amination of **3**, which was performed using Raney nickel catalyst in methanolic ammonia at room temperature for 24 h under 1000 psi hydrogen. The amine **4** was obtained in 89% yield. The third step involved heating the amine **4** with 4,7-dichloroquinoline (**5**) for 18 h at 125-130 ^{o}C in the presence of phenol and catalytic KI.[4-6] After the completion of the reaction, the liquid was diluted with methanol, and phosphoric acid was purged to get the product in salt form (Scheme 1). This process was associated with a number of limitations, which includes the use of phenol, product deterioration at high temperatures, and additional purification steps.[7] To improve the yields and overcome the limitations, some of the synthetic steps from Scheme 1 was modified.[7-12]

The HCQ synthesis was also done using the continuous flow method.[13,14] To make the displacement reaction more facile and reduce side reactions, 5-iodopentan-2-one (**7**) was employed instead of chloride analogue **1**. Tetrahydrofuran (THF) was chosen as the primary solvent to facilitate the conversion of **7** to **3** in 86% yield. In place of direct ketone reductive amination, a two-step approach using oxime was devised, allowing both reactions to be carried out in THF (Scheme 2).[13] The oxime **8** was formed by the reaction of **3** with NH_2OH in the presence of K_2CO_3 using THF as solvent. The oxime **8** was further subjected to hydrogenation with Raney nickel under high pressure to yield the compound **4**. The reaction of **4** with **5** was done in the presence of Et_3N and K_2CO_3 to get HCQ in 78% yield.[13]

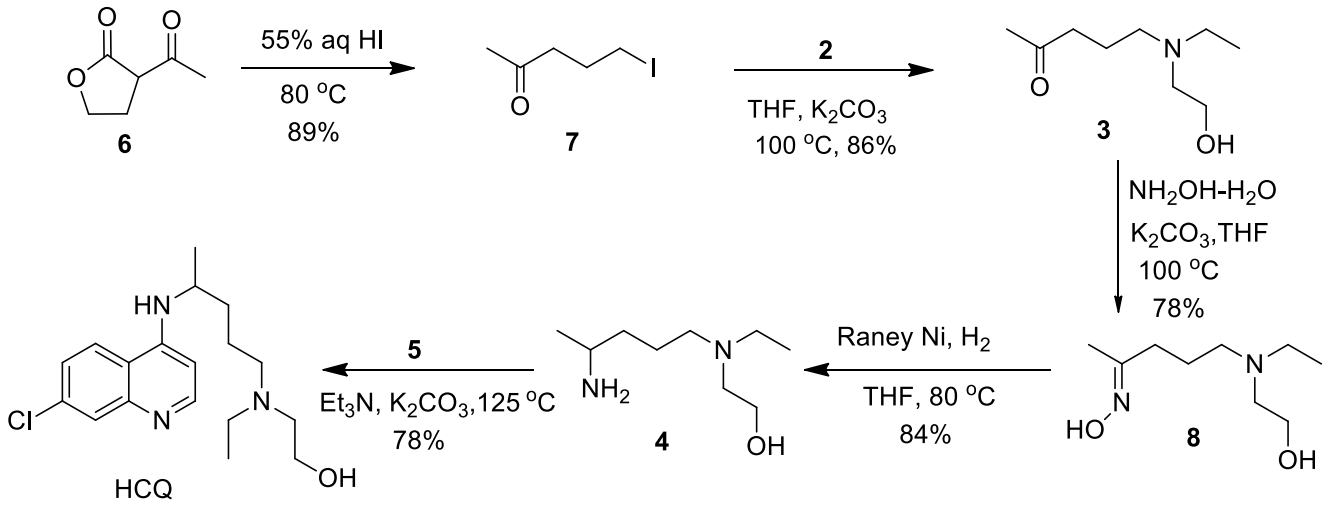
The synthesis was also done by protecting the keto group in **1** to ketal and then further reacting with amine **2**. 5-Chloro-2-pentanone (**1**) was protected by ethylene glycol in a non-polar solvent using acid catalyst like *para*-toluenesulphonic acid, methanesulphonic acid, perchloric acid etc. at a temperature ranging from 80 to 90 ^{o}C to get ketal **9** (Scheme 3).[7] This was further condensed with **2** in a non-polar solvent like toluene to give N-substituted product **10** in 83% yield. The compound **10** was deprotected

with conc. HCl to give 5-[ethyl(2-hydroxyethyl)amino]-2-pentanone (**3**), which was ammoniated and hydrogenated with Raney nickel in high pressure to give **4**.

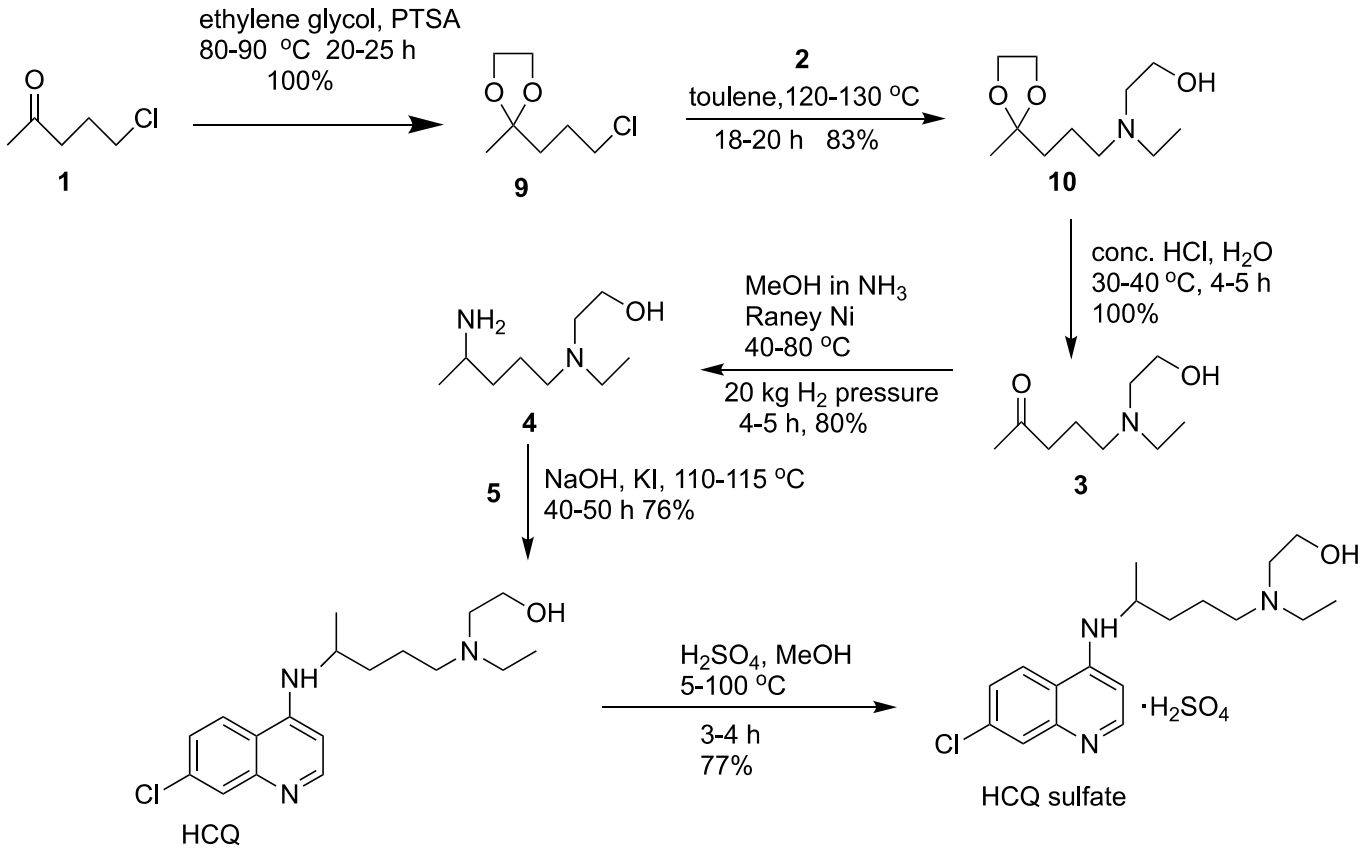
The reductive amination was carried out by the reaction of ketone **3** with alcoholic ammonia in the presence of catalyst, Raney nickel, under hydrogen pressure of 20 to 22 kg/cm^2 at temperature ranging from 40 to 80 ^{o}C for a period of 5 h to yield the compound **4** in 80% yield. Further, the reaction of **4** with **5** under basic conditions afforded HCQ in an overall yield of 40% after six stages of reactions.[7] The condensation reaction was carried out at temperature range of 110 – 115 ^{o}C for a period of more than 40 h in the presence of catalytic amount of potassium iodide and the sodium hydroxide.[7] The conversion of HCQ to HCQ sulfate was achieved by heating the HCQ in methanol with sulfuric acid at 100 ^{o}C for 4 h. The reaction of **4** and **5** was also done in nitrogen atmosphere at high pressure, resulted in the formation of HCQ (Scheme 4).[8] This reaction was done in a high-pressure reactor where both the reactants **4** and **5** in a molar ratio of 1.1:1 were present. The nitrogen gas was used to modify the reactor's internal pressure to a range of 5 to 20 bars, ideally 10 to 15 bars and the reactor is stirred at 80 ^{o}C for 30 min. Slowly the temperature was raised to 110 ^{o}C and kept for 4 h to yield HCQ in 78% yield.[8] The current procedure permits the manufacturing of HCQ with high purity and high yield while offering a number of benefits, including the inhibition of by product formation by lowering a reaction temperature and greatly shortening a reaction time by utilising pressure without the need of a catalyst or reaction solvent, as well as lower production costs.[8]



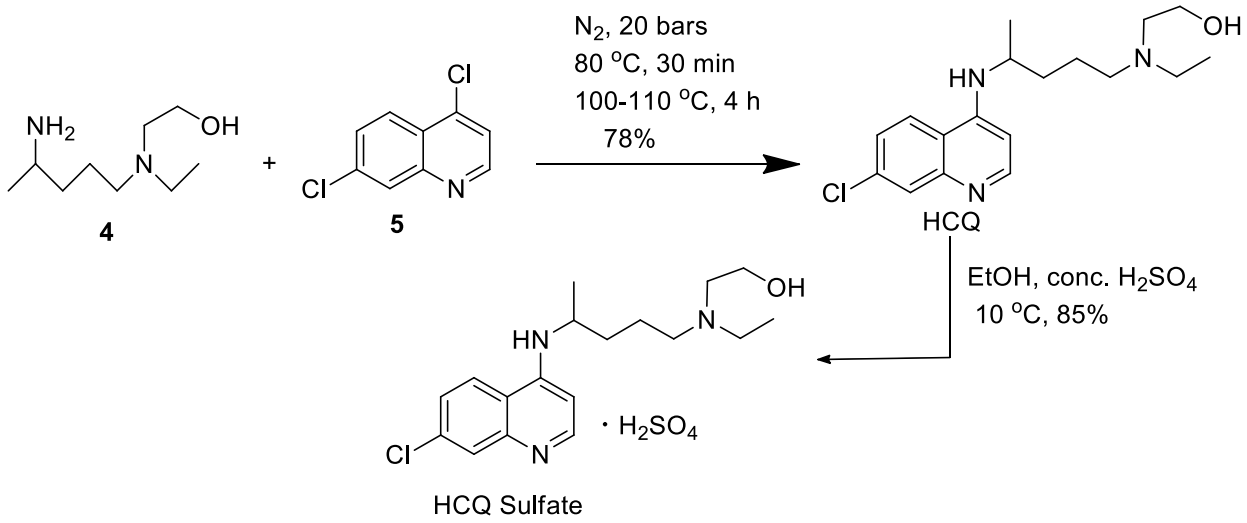
Scheme 1. Synthesis of HCQ phosphate



Scheme 2. HCQ through flow synthesis



Scheme 3. Method for preparation of HCQ sulfate[7]



Scheme 4. Synthesis of HCQ sulfate[8]

3. MEDICINAL APPLICATIONS OF HYDROXYCHLOROQUINE

3.1 ANTI-MALARIAL ACTIVITY

HCQ was the first-line treatment for malaria for decades because of its great efficacy, tolerance, and low cost.[15-18] HCQ is lipophilic, and hence it can enter red blood cells and act as a blood schizonticide against trophozoites (RBCs).[19,20] The amino acids required for development are obtained by trophozoites in RBCs breaking down haemoglobin in their food vacuole. Haem (ferriprotoporphyrin IX) is produced during this breakdown, and it is harmful to the parasite because it lyses cell membranes.[21] Harmful haem is converted to non-toxic crystallized hemozoin in the food vacuole.[22] The pH of the food vacuole is raised by HCQ, which prevents harmful haem from being converted to non-toxic hemozoin.[23] Membrane lysis and parasite death are caused by toxic haem accumulation.

The main explanation for the anti-malarial mechanism is that the detoxifying process in *Plasmodium* parasites is blocked.[24] *Plasmodium* ingests haemoglobin from the RBC cytosol into the food vacuole during the blood stage and decomposes haemoglobin to get amino acids proteins synthesis that is required for their development.[25] The parasite's heme polymerase converts toxic oxidised heme carrying ferriprotoporphyrin IX (FPIX) hematin into nontoxic crystalized polymers called as hemozoin from the proteolytic breakdown of haemoglobin.[26] Since the food vacuole is a lysosomal isolated acidic compartment, HCQ's mild alkalinity may aid its diffusion across the membrane, where it then converts to a protonated form that cannot diffuse out.[27] HCQ has been demonstrated to limit FPIX detoxification through a variety of methods. By polymerizing with FPIX, which is extremely toxic and causes parasite cell lysis, accumulating CQ in the feeding vacuole might limit FPIX polymerization.[28] It is found that the HCQ-hematin combination may cap the expanding hemozoin polymer and prevent further polymerization, leading to toxic hematin build-up and parasite damage.[29] HCQ can also be thought of as a target for enzymes involved in hemozoin production. *P.*

falciparum's histidine-rich protein-2 (Pfhrp2) has been reported to facilitate the synthesis of hemozoin *via* binding to FPIX.[30] HCQ was shown to displace FPIX from Pfhrp2 and create a CQ-FPIX complex, causing parasite cell toxicity.[31]

HCQ's target, according to another theory, is the nucleus, not the lysosome. HCQ may interact with or directly bind to DNA and RNA, disrupting the replication and transcription processes hence potentially inhibiting parasite growth and reproduction or inducing apoptosis.[32] There are also disagreements over the mechanism of HCQ uptake. HCQ build-up in parasite cells may be mediated by an importing transporter rather than diffusion. It was found that a Na^+/H^+ exchanger on the cytoplasmic membrane can work as HCQ importer, transporting HCQ and Na^+ into cells *via* proton exchange. The observation of HCQ absorption inhibition by Na^+/H^+ exchanger (NHE) inhibitors corroborated this idea.[33]

3.2 REPURPOSING OF HYDROXYCHLOROQUINE

3.2.1 Anti-cancer activity

The repurposing of HCQ for cancer therapy have been studied as autophagy regulator to target tumors.[34,35] This has been observed that cancer genesis and development is supported by autophagy which is going to be an excellent target for cancer treatment. Antimalarial medicines affect lysosomal activity, autophagy, and signaling pathways directly at the molecular level.[29] The mechanism of action, like that of other immune system treatment strategies, is likely context-dependent (i.e., depending on inflammatory conditions and/or injured tissues or organs). Autophagy and lysosomal activity inhibition is one of HCQ's main modes of action.[36] This has been established that HCQ accumulates in lysosomes and inhibits their activity (lysosomotropism). Interfering with lysosomal function may decrease lymphocyte function and have immunomodulatory or anti-inflammatory effects. HCQ inhibits the autophagic flux. Being a permeable, non-protonated, basic and weak diprotic molecule at pH 7.4, can enter cells.[37] Upon entering the lysosomes, HCQ being weakly basic amines become protonated, which leads to its entrapment in acidic lysosomes and an increase in the lysosomal pH, which inhibits the lysosomal degradative enzymes.[38,39] This interrupts the fusion of the autophagosome with the lysosome, during the formation of autophagic autolysosomes.

Antigen presentation through the lysosomal pathway is a mechanism *via* which HCQ may have anti-inflammatory effects. Hydrolytic enzymes in lysosomes work with other vesicles to digest cargo (such as organelles) and material from within the cell (through autophagy) or material from outside the cell (*via* phagocytosis) (by endocytosis or phagocytosis). Lysosomes have more role to play than only cellular substrate recycling.[40] These are also antigen processing and MHC class II presentation, which supports immune activation.[41] Antigen presentation and immunological activation are also aided by autophagy.[42-44] Because the pH of lysosomes is optimum for lysosomal enzymes involved in hydrolysis,

HCQ may disrupt lysosome and autophagosome maturation and limit antigen presentation along the lysosomal route by raising the pH of endosomal compartments.[45] Overall, the research suggests that HCQ impairs or inhibits lysosomal and autophagosome processes, resulting in immunological activation. Researchers are aiming to define the exact molecular targets of HCQ within the lysosome, in addition to lysosomotropism. In one study, PPT1, an enzyme involved in the breakdown of lipid-modified proteins, was discovered to be a potential lysosomal target of HCQ and its derivatives.[46] PPT1 is overexpressed in the synovial tissue of people with rheumatoid arthritis (RA),[47] and HCQ can bind to it and inhibit its activity.[46]

3.2.2 Anti-rheumatic activity

A common immunosuppressant prescribed for the treatment of RA is HCQ.[48] A study showed that HCQ inhibited Tfh cells *ex-vivo* and *in-vivo*, which are responsible for RA development.[49] The presence and persistence of RA are strongly linked to dendritic cells (DC) function,[50] and results demonstrated that the modulation of DC function may be an effective tool for treating RA.[51-53] The effects of HCQ are often observed to be different from the effects of glucocorticoids and nonsteroidal anti-inflammatory agents as the fact that HCQ improves clinical and laboratory parameters, however, sets them apart due to their slow onset of action. The effects of HCQ upon pH in intracellular vacuoles, in addition to proteins being degraded by acidic hydrolases in the lysosome, macromolecules being assembled in endosomes, and proteins being modified post-translationally in the Golgi complex, are altered.

Anti-rheumatic effects are observed by HCQ by interfering with "antigen processing" within macrophages and other antigen-presenting cells. To digest antigenic proteins and assemble peptides with the α and β chains of MHC class II proteins, acidic cytoplasmic compartments are needed. Anti-malarials reduce the formation of the complexes of peptides and MHC proteins required for $CD4^+$ T cells to be stimulated and also reduce the immune response against autoantigenic peptides. Anti-malarials are particularly well suited for combination drug therapy, because their mechanism of action differs from those of other anti-rheumatic medications, triple treatment with HCQ, methotrexate, and sulfasalazine was nearly as beneficial in terms of quality of life as biologic treatment.[54] The acidic vesicles, like the lysosomal compartment, collect HCQ (an essential site of action for this drug)[55,56] due to its weak base. In patients with RA with mild joint symptoms, HCQ blood concentrations were shown to be higher than in those with active seropositive disease. An individual's condition, like apparent or subclinical inflammation (an acidic milieu) that sequesters these drugs, may also influence drug level variations. DCs were shown to be active in and CIA mice and RA patients, according to a study, and HCQ blocked DC activities, preventing the onset and progression of RA. The mechanism could be linked to toll-like receptors (TLR9) inhibition.[57] The study also suggested that the HCQ use lowers the risk of diabetes in rheumatoid arthritis patients.[58] This is

linked to improved lipid profiles in these patients.[59] In individuals with inflammatory rheumatic disorders, HCQ can lower atherosclerosis rates, improve hyperglycemia and hyperlipidemia, and protect against infections.[60,61]

HCQ medication appears to have no higher risk in the short term among individuals with rheumatoid arthritis, but it appears to be associated with greater cardiovascular mortality in the long run, according to a study. Even in the short term, the addition of azithromycin raises the risk of heart failure and cardiovascular death.[62] In a study of clinical and structural efficacy, HCQ was found to be comparable to or less effective than methotrexate or sulfasalazine in monotherapy. Combining HCQ with other DMARDs may improve clinical efficacy.[63]

3.2.3 Epigenetic activity

Multiple myeloma (MM) is a haematological tumour produced through a combination of genetic and epigenetic alterations where neoplastic plasma cells (PCs) grow and concentrate in the bone marrow (BM).[64] The pathophysiology of this tumour has been connected to the hyperactivation of a multi-subunit oncogenic histone methyltransferase, the Polycomb repressive complex 2 (PRC2). PRC2 is a methyltransferase that catalyzes the monomethylation, dimethylation, and trimethylation of histone H3 at lysine 27 (H3K27me3), which is required for cellular differentiation and vertebrate development.[65] The anti-malarial medicine HCQ, commonly known as an autophagy inhibitor, has a new mode of action, which could explain its anti-cancer effectiveness.

Multiple myeloma (MM) development and progression have been linked to a number of genetic and epigenetic events. This is also associated as deregulation of a number of signaling pathways which control RNA editing, DNA repair, and protein homeostasis, and that could be used as therapeutic targets.[66-70] According to a study, HCQ inhibits PRC2 allosteric binding to embryonic ectoderm development (EED) within the H3K27me3-binding pocket, antagonizing PRC2 catalytic activity. The *in-silico* results back up HCQ's claim that it lowers H3K27me3 levels in MM cells. These data suggest that HCQ plays a different epigenetic role, which could have clinical ramifications.

3.2.4 Systemic Lupus Erythematosus (SLE)

SLE is a chronic multisystem autoimmune illness where the healthy tissues have been attached by mistake from the immune system of the body. It is a complex and heterogeneous illness that can cause inflammation in practically every tissue or organ of the body.[71] In addition to severe constitutional symptoms, SLE is most usually linked with skin, joint, serosal, renal, and central nervous system manifestations. The condition is particularly frequent in young women, and it is still linked to a higher mortality rate and a death rate.[72]

With novel drugs, such as targeted biological treatments, being designed and extensively studied, there's been a revival of interest in SLE in the latest years.[73] Moreover, several of the drugs being used to treat SLE for many years are all being re-examined. Immunomodulatory therapies used in maintenance and induction of remission in lupus nephritis, such as azathioprine, cyclophosphamide, and mycophenolate mofetil, are in specific being thoroughly explored, as evidenced by the latest systematic review,[74] and this recent finding has contributed to the development of robust treatment guidelines of lupus nephritis.[75] Similar evidence is being sought in lupus symptoms other than renal.[76]

The anti-malarial HCQ has been a standard treatment for SLE. It is hypothesized to help SLE patients by stabilizing the microsomal membrane, which prevents endosomal maturation and neutralizes the acidic environment crucial for endosomal activity.[77] For maximum function, intracellular TLRs need to attach to nucleic acid ligands, and this action is aided by the acidic endosome environment, which is disturbed by HCQ.[77] When TLRs are inhibited, levels of interferon-alpha, a cytokine considered to be one of the key mediators of inflammation, are suppressed. In SLE,[78] there are very few reported instances of severe side effects with HCQ, most of which self-limiting and mild, like headaches and nausea. It is usually dosed weight based at a dose of 6.5 mg/kg, to a maximum daily dose of 400 mg, either as a single dose or as a divided dose.

In SLE, HCQ inhibits Toll-like receptor activation.[79] Blocking this pathway appears to decrease the body's primary cell-mediated inflammatory response *in-vitro*, while *in-vivo* results showed lower levels of interferon-alpha.[78] This is due to the HCQ's powerful influence on the cell-mediated pattern of inflammation present in lupus. Due to the positive response with HCQ in SLE, this is anticipated that the drug will expand markedly.[78,80-82]

3.2.5 Repurposing for COVID-19

Several studies have demonstrated that HCQ has antiviral properties, which has sparked curiosity about its utility in coronavirus disease 2019 (COVID-19).[83–88] Several therapies are being tested to determine their effectiveness against SARS-CoV-2 (SARS-CoV-2) as a consequence of the COVID-19 pandemic. HCQ inhibits inflammation by inhibiting the production of cytokines and inhibiting immunomodulation.[2,89,90] Within a rheumatic setting and potentially in cases of SARS-CoV-2 infection, attenuation of inflammation results in greater responses.[91] HCQ increases the pH of lysosomes to inhibit endosomal acidification, thereby preventing viral RNA from being shed into the cytoplasm and interfering with replication.[84,92,93] The *in-vitro* study with HCQ for SARS-CoV-2 showed an EC_{50} value of 6.14 μM after 24 h of growth.[86,94] There are many trials registered to treat or prevent COVID-19 for HCQ, either alone or in combination with other drugs (Clinicaltrials.gov). The HCQ showed an excellent 537 h half-life in blood and 2963 h in plasma.[95] The clinical trial doses vary for 7-14 days daily from

200-400 mg either once or twice.

The HCQ also acts as Sialic Acid Receptors (SAR) blockage, which is helpful against SARS-CoV-2.[92,96,97] This has been found that the region of the S protein that is responsible for SARS-CoV-2 binding to sialic acid receptors is similar to the region that is responsible for MERS-CoV attachment to SAR.[96] The SAR and the previously known ACE2 receptor may contribute to SARS-CoV-2's entry into the upper respiratory tract. Additionally, a novel binding site for gangliosides was discovered in the N-terminal domain (NTD) of the SARS-CoV-2 S protein. HCQ was effective in inhibiting SAR.[93]

The HCQ also showed its action by acting on ACE2 receptor, which works at the pre-entry stage only.[98,99] The S proteins have a role in viral particle association and passage into host cells.[100] It is made up of two parts: the S1 subunit and the S2 subunit.[101] The S1 subunit is in charge of facilitating passage into host cells by binding to the ACE2 receptor. After that, cellular proteases like transmembrane serine protease II (TMPRSS2) aid S priming, resulting in S1/S2 and S2' breakage. Splice changes in the genome of TMPRSS2 caused by single-nucleotide polymorphisms have been shown to modify its expression levels, influencing the rate of SARS-CoV-2 infection in patients.[102] The S2 domain is cleaved, releasing fusion peptide[103] and S2 subunit promotes the viral membrane to merge with the cellular membrane.[94] SARS-CoV-2 spikes linked to a truncated ACE2 with a greater affinity than full-length ACE2, according to a new in silico investigation. The N-terminal region of this shortened ACE2 was identical to that of full-length ACE2.[97] Some other research identified the key amino acid acids responsible for increased spike binding affinity to ACE2.[105] For ACE2 to be converted to an active form, it must be glycosylated. As a result, when the SARS-CoV-2 S protein attaches to it, the ACE2 receptor is activated by glycosylation. In this scenario, HCQ is critical because it blocks the glycosylation of ACE2 receptors, which prevents SARS-CoV2 from infecting host organisms.[106]

4. CONCLUSION

Hydroxychloroquine (HCQ) belongs to the 4-aminoquinoline family. This molecule has proven its utility for the treatment of many diseases that have been recognized by WHO also. HCQ has been an anti-malarial drug and is also used for the treatment of autoimmune and rheumatic diseases. This molecule is repurposed for many types of diseases, either alone or in combination with other drugs. The studies for the use of HCQ as anti-cancer activity, anti-rheumatic activity, epigenetic activity, systemic lupus erythematosus, and in recent COVID-19 have been covered. The synthesis of HCQ has been discussed using 4,7-dichloroquinoline.

ACKNOWLEDGEMENT

The authors are thankful to their respective institutions for infrastructural support. The author Nidhi Yadav performed the literature search, Y. K. Tyagi done part of writing and analyzing, and R. Singh gave the idea and critically worked on the manuscript.

REFERENCES

1. K. D. Rainsford, A. L. Parke, M. Clifford-Rashotte, and W. F. Kean, *Inflammopharmacology*, 2015, **23**, 231.
2. E. Schrezenmeier and T. Dörner, *Nat. Rev. Rheumatol.*, 2020, **16**, 155.
3. E. Carafoli, *Biochem. Biophys. Res. Commun.*, 2021, **538**, 156.
4. A. R. Surrey, *U.S. Patent*, 2546658, 1951.
5. A. R. Surrey and H. F. Hammer, *J. Chem. Soc.*, 1950, **72**, 1814.
6. R. Shaik and H. S. P. Rao, *Mini-Rev. Org. Chem.*, 2022, **19**, 111.
7. A. Kumar, K. D. Vyas, D. Singh, S. Nandavadekar, S. Bhise, and A. Jadhav, *Int. Patent Appl.*, WO2005/062723 A2, 2005.
8. Y. S. Min, H. S. Cho, and K. W. Mo, *Int. Patent Appl.*, WO2010/027150 A2, 2010.
9. H. You, Y. Liu, F. Ning, Z. Zheng, Q. Yu, X. Niu, and C. Li, *Chinese Patent Appl.*, CN104803859A, 2015.
10. M. Tang, D. Gong, Z. Yang, Y. Liu, J. Yang, Z. Cai, and Z. Zha, *Chinese Patent Appl.*, CN104230803, 2017.
11. J. Pi, Y. Ding, R. Yue, J. Wei, W. Pan, and G. Xie, *Chinese Patent Appl.*, CN103724261, 2014.
12. P. M. Blaney, S. J. Byard, G. Carr, G. J. Ellames, J. M. Herbert, J. E. Peace, D. I. Smith, W. F. Michne, and M. S. Sanner, *Tetrahedron: Asymmetry*, 1994, **5**, 1815.
13. E. Yu, H. P. R. Mangunuru, N. S. Telang, C. J. Kong, J. Verghese, S. E. Gilliland III, S. Ahmad, R. N. Dominey, and B. F. Gupton, *Beilstein J. Org. Chem.*, 2018, **14**, 583.
14. B. K. Gupton, A. Saeed, H. P. R. Mangunure, and N. S. Telang, US20200407321A1, 2019.
15. E. O. Titus, *Ther. Drug Monit.*, 1989, **11**, 369.
16. E. Pussard and F. Verdier, *Fundam. Clin. Pharmacol.*, 1994, **8**, 1.
17. C. Verbaanderd, H. Maes, M. B. Schaaf, V. P. Sukhatme, P. Pantziarka, V. Sukhatme, P. Agostinis, and G. Bouche, *Ecancermedicalscience*, 2017, 781.
18. I. Law, K. F. Ilett, L. P. Hackett, M. Page-Sharp, F. Baiwog, S. Gomorrai, I. Mueller, H. A. Karunajeewa, and T. M. Davis, *Br. J. Clin. Pharmacol.*, 2008, **65**, 674.
19. D. A. Baker, *Mol. Biochem. Parasitol.*, 2010, **172**, 57.
20. S. M. Abay, *Parasit. Vectors*, 2013, **6**, 1.

21. D. Plantone and T. Koudriavtseva, *Clin. Drug Investig.*, 2018, **38**, 653.
22. A. F. G. Slater and A. Cerami, *Nature*, 1992, **355**, 167.
23. A. H. Mackenzie, *Am. J. Med.*, 1983, **75**, 5.
24. R. Thomé, S. C. P. Lopes, F. T. M. Costa, and L. Verinaud, *Immunol. Lett.*, 2013, **153**, 50.
25. N. Mohandas, *Med. Microbiol. Immunol.*, 2012, **201**, 593.
26. A. C. Chou and C. D. Fitch, *Life Sci.*, 1992, **51**, 2073.
27. D. J. Krogstad and P. H. A. Schlesinger, *Biochem. Pharmacol.*, 1986, **35**, 547.
28. C. D. Fitch, R. Chevli, H. S. Banyal, G. Phillips, M. A. Pfaller, and D. J. Krogstad, *Antimicrob. Agents Chemother.*, 1982, **21**, 819.
29. D. J. Sullivan Jr., I. Y. Gluzman, and D. E. Goldberg, *Science*, 1996, **271**, 219.
30. D. J. Sullivan Jr., I. Y. Gluzman, D. G. Russell, and D. E. Goldberg, *Proc. Natl. Acad. Sci. U.S.A.*, 1996, **93**, 11865.
31. A. V. Pandey, H. Bisht, and V. K. Babbarwal, *Biochem. J.*, 2001, **355**, 333.
32. G. D. Li, *Med. Hypotheses*, 2006, **67**, 323.
33. C. P. Sanchez, S. Wünsch, and M. Lanzer, *J. Biol. Chem.*, 1997, **272**, 2652.
34. G. Manic, F. Obrist, G. Kroemer, I. Vitale, and L. Galluzzi, *Mol. Cell. Oncol.*, 2014, **1**, e29911.
35. F. Bu, J. Zhang, W. Shuai, J. Liu, Q. Sun, and L. Ouyang, *Drug Disc. Today*, 2022, **27**, 1815.
36. E. L. Nirk, F. Reggiori, and M. Mauthe, *EMBO Mol. Med.*, 2020, **12**, 12476.
37. V. B. Randolph, G. Winkler, and V. Stollar, *Virology*, 1990, **174**, 450.
38. M. Wibo and B. Poole, *J. Cell Biol.*, 1974, **63**, 430.
39. R. Sakthiswary and E. Suresh, *Lupus*, 2014, **23**, 225.
40. A. Ballabio and J. S. Bonifacino, *Nat. Rev. Mol. Cell Biol.*, 2020, **21**, 101.
41. V. Lotteau, L. Teyton, and A. Peleraux, *Nature*, 1990, **348**, 600.
42. G. Ghislat and T. Lawrence, *Cell. Mol. Immunol.*, 2018, **15**, 944.
43. C. Münz, *Trends Immunol.*, 2016, **37**, 755.
44. J. M. Ireland and E. R. Unanue, *J. Exp. Med.*, 2011, **208**, 2625.
45. S. Ohkuma and B. Poole, *Proc. Natl. Acad. Sci. U.S.A.*, 1978, **75**, 3327.
46. V. W. Rebecca, M. C. Nicastri, C. Fennelly, C. I. Chude, J. S. Barber-Rotenberg, A. Ronghe, Q. McAfee, N. P. McLaughlin, G. Zhang, A. R. Goldman, and R. Ojha, *Cancer Discov.*, 2019, **9**, 220.
47. C. Ma, Q. Lv, S. Teng, Y. Yu, K. Niu, and C. Yi, *Int. J. Rheum. Dis.*, 2017, **20**, 971.
48. C. C. Mok, H. J. Penn, K. L. Chan, S. M. Tse, L. J. Langman, and P. J. Jannetto, *Arthritis Care Res.*, 2016, **68**, 1295.
49. J. Han, Q. Zhou, X. Li, J. He, Y. Han, H. Jie, Y. He, and E. Sun, *Biomed. Pharmacother.*, 2018, **97**,

838.

50. J. Dieker, J. Tel, E. Pieterse, A. Thielen, N. Rother, M. Bakker, J. Fransen, H. B. Dijkman, J. H. Berden, J. M. de Vries, and L. B. Hilbrands, *Arthritis Rheumatol.*, 2016, **68**, 462.
51. Y. Han, X. Li, Q. Zhou, H. Jie, X. Lao, J. Han, J. He, X. Liu, D. Gu, Y. He, and E. Sun, *J. Immunol.*, 2015, **195**, 4126.
52. X. Li, Y. Han, Q. Zhou, H. Jie, Y. He, J. Han, J. He, Y. Jiang, and E. Sun, *J. Cell. Mol. Med.*, 2016, **20**, 170.
53. J. He, X. Li, J. Zhuang, J. Han, G. Luo, F. Yang, Y. Sun, P. Liao, Y. Han, Y. He, and H. Shi, *J. Immunol.*, 2018, **201**, 3514.
54. H. Jalal, J. R. O'Dell, S. L. Bridges Jr., S. Cofield, J. R. Curtis, T. R. Mikuls, L. W. Moreland, and K. Michaud, *Arthritis Care Res.*, 2016, **68**, 1751.
55. D. A. Fishbain, J. Trescott, B. Cutler, E. Abdel-Moty, R. S. Rosomoff, and H. L. Rosomoff, *J. Acad. Consult. Liaison Psychiatry*, 1993, 355.
56. S. Tett, A. McLachlan, R. Day, and D. Cutler, *Agents Actions. Suppl.*, 1993, 145.
57. J. Han, X. Li, X. Luo, J. He, X. Huang, Q. Zhou, Y. Han, H. Jie, J. Zhuang, Y. Li, and F. Yang, *Biomed. Pharmacother.*, 2020, **132**, 110848.
58. A. Bili, J. A. Sartorius, H. L. Kirchner, S. J. Morris, L. J. Ledwich, J. L. Antohe, S. Dancea, E. D. Newman, and M. C. M. Wasko, *J. Clin. Rheumatol.*, 2011, **17**, 115.
59. S. J. Morris, M. C. M. Wasko, J. L. Antohe, J. A. Sartorius, H. L. Kirchner, S. Dancea, and A. Bili, *Arthritis Care Res.*, 2011, **63**, 530.
60. C. Rempenault, B. Combe, T. Barnetche, C. Gaujoux-Viala, C. Lukas, J. Morel, and C. Hua, *Ann. Rheum. Dis.*, 2018, **77**, 98.
61. G. Ruiz-Irastorza, N. Olivares, I. Ruiz-Arruza, A. Martinez-Berriotxoa, M. V. Egurbide, and C. Aguirre, *Arthritis Res. Ther.*, 2009, **11**, 1.
62. T. W. Huizinga and R. Knevel, *Lancet Rheumatol.*, 2020, **2**, e652.
63. C. Rempenault, B. Combe, and T. Barnetche, *Arthritis Care Res.*, 2020, **72**, 36.
64. A. Romano, C. Conticello, M. Cavalli, C. Vetro, A. L. Fauci, N. L. Parrinello, and F. D. Raimondo, *Biomed. Res. Int.*, 2014, 198539.
65. L. Di Croce and K. Helin, *Mol. Biol.*, 2013, **20**, 1147.
66. G. Morgan, B. Walker, and F. Davies, *Nat. Rev. Cancer*, 2012, 335.
67. N. Amodio, D'Amodio, G. Passarino, P. Tassone, and D. Bellizzi, *Expert Opin. Ther. Targets*, 2017, **21**, 91.
68. L. Raimondi, A. De Luca, E. Morelli, G. Giavaresi, P. Tagliaferri, P. Tassone, and N. Amodio, *BioMed Res. Int.*, 2016, 6504593.

69. M. Rossi, M. Teresa Di Martino, E. Morelli, M. Leotta, A. Rizzo, A. Grimaldi, G. Misso, and M. Caraglia, *Curr. Cancer Drug Targets*, 2012, **12**, 757.
70. N. Amodio, M. T. Di Martino, A. Neri, P. Tagliaferri, and P. Tassone, *Expert Opin. Biol. Ther.*, 2013, **13**(supl), S125.
71. F. Basta, F. Fasola, K. Triantafyllias, and A. Schwarting, *Rheumatol. Ther.*, 2020, **7**, 433.
72. M. B. Urowitz, D. D. Gladman, B. D. Tom, D. Ibanez, and V. T. Farewell, *J. Rheumatol.*, 2008, **35**, 2152.
73. E. M. Ginzler, D. J. Wallace, J. T. Merrill, R. A. Furie, W. Stohl, W. W. Chatham, A. Weinstein, J. D. McKay, W. J. McCune, Z. J. Zhong, and W. W. Freimuth, *J. Rheumatol.*, 2014, **41**, 300.
74. L. Henderson, P. Masson, J. C. Craig, R. S. Flanc, M. A. Roberts, G. F. Strippoli, and A. C. Webster, *Cochrane Database Syst. Rev*., 2012, CD002922.
75. B. H. Hahn, M. A. Mcmahon, A. Wilkinson, W. D. Wallace, D. I. Daikh, J. D. Fitzgerald, G. A. Karpouzas, J. T. Merrill, D. J. Wallace, J. Yazdany, and R. Ramsey-Goldman, *Arthritis Care Res.*, 2012, **64**, 797.
76. A. Kaul, C. Gordon, M. K. Crow, Z. Touma, M. B. Urowitz, R. van Vollenhoven, G. Ruiz-Irastorza, and G. Hughes, *Nat. Rev. Dis. Primers*, 2016, **2**, 16039.
77. R. Lafyatis, M. York, and A. Marshak-Rothstein, *Arthritis Rheumatol.*, 2006, **54**, 3068.
78. R. Willis, A. M. Seif, G. McGwin Jr., L. A. Martinez-Martinez, E. B. González, N. Dang, E. Papalardo, J. Liu, L. M. Vilá, J. D. Reveille, and G. S. Alarcón, *Lupus*, 2012, **21**, 830.
79. A. Kužnik, M. Benčina, U. Švajger, M. Jeras, B. Rozman, and R. Jerala, *J. Immunol.*, 2011, **186**, 4794.
80. G. S. Alarcón, G. McGwin, A. M. Bertoli, B. J. Fessler, J. Calvo-Alén, H. M. Bastian, L. M. Vilá, and J. D. Reveille, *Ann. Rheum. Dis.*, 2007, **66**, 1168.
81. G. T. Pons-Estel, G. S. Alarcón, G. McGwin Jr, M. I. Danila, J. Zhang, H. M. Bastian, J. D. Reveille, and L. M. Vilá, *Arthritis Care Res.*, 2009, **61**, 830.
82. J. C. Shee, *Lancet.*, 1953, **262**, 201.
83. E. Keyaerts, L. Vijgen, P. Maes, J. Neyts, and M. Van Ranst, *Biochem. Biophys. Res. Commun.*, 2004, **323**, 264.
84. M. J. Vincent, E. Bergeron, S. Benjannet, B. R. Erickson, P. E. Rollin, T. G. Ksiazek, N. G. Seidah, and S. T. Nichol, *Virol. J.*, 2005, **2**, 1.
85. M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, and G. Xiao, *Cell Res.*, 2020, **30**, 269.
86. X. Yao, F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, X. Liu, L. Zhao, E. Dong, C. Song, S. Zhan, R. Lu, H. Li, W. Tan, and D. Liu, *Clin. Infectious Dis.*, 2020, **71**,732.

87. J. Andreani, M. Le Bideau, I. Duflot, P. Jardot, C. Rolland, M. Boxberger, N. Wurtz, J. M. Rolain, P. Colson, B. La Scola, and D. Raoult, *Microb. Pathog.*, 2020, **145**, 104228.
88. Geetanjali, R. Srivastava, and R. Singh, *Mini-Rev. Org. Chem.*, 2022, **19**, 180.
89. R. I. Fox, *Sem. Arthritis Rheum.*, 1993, **23**, 82.
90. A. Gonzalez-Noriega, J. H. Grubb, V. Talkad, and W. S. Sly, *J. Cell Biol.*, 1980, **85**, 839.
91. N. Sinha and G. Balayla, *Postgrad. Med. J.*, 2020, **96**, 550.
92. J. Fantini, C. Di Scala, H. Chahinian and N. Yahi, *Int. J. Antimicrob. Agents*, 2020, **55**, 105960.
93. K. Gbinigie and K. Frie, *BJGP Open*, 2020, **4**, bjgpopen20X101069.
94. C. De Savi, D. L. Hughes, and L. Kvaerno, *Org. Process Res. Dev.*, 2020, **24**, 940.
95. Plaquenil Hydroxychloroquine Sulfate Tablets, USP. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/009768Orig1s 051lbl.pdf (Accessed July 17, 2022).
96. E. Milanetti, M. Miotto, L. Di Rienzo, M. Nagaraj, M. Monti, T. W. Golbek, G. Gosti, S. J. Roeters, T. Weidner, D. E. Otzen, and G. Ruocco, *Front. Mol. Biosci.*, 2021, 509.
97. Y. Huang, B. S. Harris, S. A. Minami, S. Jung, P. S. Shah, S. Nandi, K. A. McDonald, and R. Faller, *Biophys. J.*, 2022, **121**, 79.
98. A. A. Sarhan, N. A. Ashour, and A. A. Al-Karmalawy, *Inform. Med. Unlocked*, 2021, **24**, 100604.
99. J. W. Ulm and S. F. Nelson, *Transbound Emerg. Dis.*, 2021, **68**, 313.
100. M. A. Shereen, S. Khan, A. Kazmi, N. Bashir, and R. Siddique, *J. Adv. Res.*, 2020, **24**, 91.
101. S. Satarker and M. Nampoothiri, *Arch. Med. Res.*, 2020, **51**, 482.
102. S. Boopathi, A. B. Poma, and P. Kolandaivel, *J. Biomol. Struct. Dyn.*, 2021, **39**, 3409.
103. M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N. H. Wu, A. Nitsche, and M. A. Müller, *Cell*, 2020, **181**, 271.
104. A. Basit, T. Ali, and S. U. Rehman, *J. Biomol. Struct. Dyn.*, 2021, **39**, 3605.
105. G. K. Veeramachaneni, V. B. S. C. Thunuguntla, J. Bobbillapati, and J. S. Bondili, *J. Biomol. Struct. Dyn.*, 2021, **39**, 4015.
106. P. Pahan and K. Pahan, *J. Neuroimmune Pharmacol.*, 2020, **15**, 174.

Ms. Nidhi Yadav obtained her bachelor's degree from the University of Delhi, Delhi. She obtained her master's degree in chemistry from the University of Delhi, Delhi. She is pursuing Ph.D. in chemistry from Guru Gobind Singh Indraprastha University, Delhi, and Delhi Technological University since August 2019. Her research interest is in synthetic organic chemistry, medicinal chemistry, and natural product chemistry.

Dr. Yogesh K. Tyagi worked in Department of Biochemistry, VP Chest Institute, University of Delhi, Delhi and obtained his Ph.D. Degree in year 2002. He also worked as PDF in same Institute from year 2002 to 2007. In year 2007, Dr. Tyagi joined USBAS, GGSIPU, Delhi as an Assistant Professor. In Year 2004, he was awarded a Young Scientist Award by DST. He was also nominated by DST for Nobel laureate meeting at Germany. He was awarded Best Researcher Award in year 2011 by GGSIPU. His research area is Bio-organic Chemistry.

Prof. (Dr.) Ram Singh was born in Chandauli, Sitamarhi, Bihar, India. He did his schooling from Sainik School Tilaiya, India. He received his B.Sc., M.Sc. and Ph.D. from University of Delhi, India. During post-doctoral period, he worked at CEMDE, University of Delhi and Fast Track Young Scientists (DST) at Department of Chemistry, University of Delhi. At present, he is working as Professor in the Department of Applied Chemistry at Delhi Technological University since 2010. Dr. Singh has published 95 research papers, authored 11 books, 15 book chapters, 31 Modules for ePG Pathshala, and contributed in more than 100 symposia and seminars. His research interests are at the interface of chemistry, biology and biomaterials science. His group has been involved in solving challenging problems related to human health and society giving emphasis on neurodegenerative diseases like Alzheimer's and Parkinson Diseases. He is on the Editorial Advisory Board of various journals of repute and Life Member of various societies.