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A Systematic Review on Effects of Chloroquine as a Antiviral against Covid-19

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Abstract:- Coronavirus (covid-19) disease is caused by SARS-COV-2 virus,it is known as severe acute respiratory syndrome coronavirus 2, firstly seen in china in December 2019in human it is characterized by pulmonary infection.The intension of this systematic review was to encapsulate the evidence regarding chloroquine efficacy for the covid -19 treatment.

Chloroquine is part of WHO (World health organization) essential medicine model list and it is set clinical safety profile and it is also cheap and has been worldwide used for additionally 70 years.Chloroquine has many activities, one of which is to alkalise the phagolysosome, which hampers the low-pH-dependent steps of viral replication, including uncoating and fusion, In vitro study revealed that Chloroquine is effective at both entry, and at post entry stages of SARS-COV-2 infection in Vero E6 cells. In vitro, chloroquine appears as a versatile bioactive agent reported to possess antiviral activity against RNA viruses as diverse as rabies virus ,Dengue virus , HIV ,hepatitis C virus, hepatitis A virus, poliovirus , influenza A and B viruses, Zika virus, influenza A H5N1 virus, Chikungunya virus , as well as various DNA viruses such as hepatitis B virus and herpes simplex virus.chloroquine is effective in reducing viral replication in other infections , including SARS-associated coronavirus (COV)and MERS-COV.

Keywords:- *SARS-COV-2, Chloroquine, Coronavirus, Severe Acute Respiratory Syndrome*

I. INTRODUCTION

An issue that concerns people all across the world is the coronavirus. Approximately 15% of cases of severe contaminations (Wu and MCGOOGAN, 2020) are observed in patients (1), along with side effects such a wide range of respiratory disease side effects, including hack, fever, and windedness, from asymptomatic or extraordinarily mild to severe pneumonia. Although in-vitro tests have suggested that chloroquine, which is typically used as an antimalarial and is also used as an immunomodulator, is effective in reducing viral replication in other infections, including MERS-COV and SARS-related Covid (COV), there is no known powerful, explicit, demonstrated pharmacological therapy during this pandemic (2-4). Chloroquine was created by Bayer in Germany in 1934 and emerged apparently quite some time ago as a potent alternative for conventional quinine. Chloroquine is an amine acidotropic form of quinine (5). Quinine, a substance found in the bark of the native Peruvian cinchona tree, has lately been used as an antimalarial (6). For a decade, chloroquine has been a first-line treatment and preventative measure for jungle fever, and it is the most often prescribed medication worldwide (7). Chloroquine does not cure pneumonia, but it does prevent future infection by preventing viral multiplication. Chloroquine is used in combination with the antitoxin azithromycin to treat pneumonia. According to several researchers, aspiratory fibrosis is the primary cause of pneumonia caused by Coronavirus 19. This is one of the main causes of why breathing air into the lungs doesn't increase their capacity (8).

Chloroquine and the 4-aminoquinoline drug hydroxychloroquine belong to the same subatomic family. The N-ethyl substituent is -hydroxylated, which distinguishes hydroxy-chloroquine from chloroquine by the presence of a hydroxyl group at the end of the side chain. This substance is available as hydroxychloroquine sulphate for oral use. The pharmacokinetics of hydroxychloroquine are similar to those of chloroquine, with rapid gastrointestinal retention and renal end. Nevertheless, there are some differences in the clinical symptoms and negative effects of these drugs. Because of its toxicity at high dosages, the indication for chloroquine in jungle fever was either a high dose for a limited period of time or a low dose for an extended period of time. Hydroxychloroquine was predicted to be less hazardous and almost as effective as chloroquine against Plasmodium falciparum jungle fever, however due to its physicochemical features, it is much less effective than chloroquine against P. falciparum that is resistant to chloroquine. The advantage of hydroxychloroquine is that it frequently results in great resilience when used in large dosages over extended periods of time. Sadly, due of the constant emergence of P. falciparum strains that are chloroquine-safe, the effectiveness of chloroquine gradually decreased (9). One of the several actions of chloroquine is to alkalize the phagolysosome, which prevents viral replication's low-pH-dependent steps, such as combination and uncoating (10).

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II. PHYSICAL PROPERTIES OF CHLOROQUINE

Chloroquine is a tasteless, bitter, white or slightly yellow crystalline powder. Its IUPAC name is 4-N-(7-chloroquinolin-4-yl)-1-N,1-N-diethylpentane-1,4-diamine and its chemical formula is C18H26ClN3. It is soluble in diluted acids, chloroform, and ether but only very weakly soluble in water. The pH of a 10% solution of chloroquine phosphate ranges from 3.5 to 4.5. The maxima and minima of the UV spectrum of chloroquine in neutral methanol solution are 218 nm, 253 nm, and 328 nm, respectively, and 243 and 275 nm, respectively. On a Varian T6-A NMR spectrometer using deuterated chloroform (CDCl3) and heavy water (D2O), respectively, as solvents and tetramethylsilane as an internal reference, the 1H-nuclear magnetic resonance (NMR) spectra of chloroquine base and phosphate were obtained (11).

➢ *Structure of Chloroquine:-*

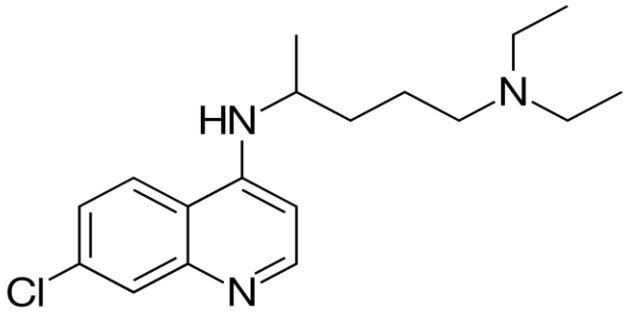

Fig 1 Structure of Chloroquine

➢ *Synthesis of Chloroquine:-*

Chloroquine is one of the first and most effective antimalarials. The essential intermediate in its mix is 4, 7-dichloroquinoline, which is formed from 7, 4-chloro-4-quinolone (11). The natural compound quinine from cinchona tree bark was used as an antimalarial specialist prior to the union of chloroquine. Methylene blue, a colour that may selectively kill jungle fever parasites, was discovered in 1891 by Paul Ehrlich's group. Pamaquine, a more effective antimalarial specialist, was created by modifying the fundamental methyl bunch using science and building movement connections. The acridine subordinate quinacrine, which contains an extra benzene ring, was formed as a result of the linkage of pamaquine's primary side chain to a few distinct heterocyclic ring structures. Two CQ analogues, soitoquine and primaquine, which were more effective and superior antimalarial medications, were discovered as a consequence of more study (12). Then, research on these substances produced the discovery of ResochinR. Research on ResochinR during World War II resulted in the creation of CQ. (13)

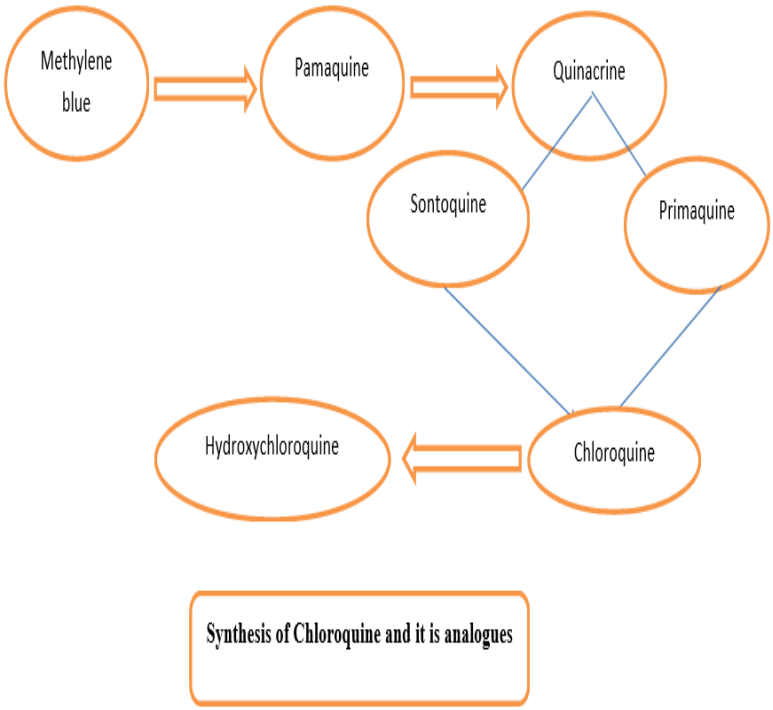

Fig 2 Synthesis of Chloroquine and it's analogues

➢ *Mode of action of chloroquine against Covid-19:-*

Unprotonated chloroquine may easily diffuse through cell membranes to acidic vesicles in the cytoplasm, such as lysosomes and late endosomes, and after being protonated, it becomes stuck in the vesicles. Protonated chloroquine is held in the cellular compartments by hydrolases, preventing it from diffusing out of the lysosome or endosome. In accordance with the Henderson-Hasselbalch rule, chloroquine and its analogues are diprotic weak bases that can preferentially enter lysosomes where they get protonated in a way inversely proportional to pH. (14,15). The term "lysosomotropic agents" refers to them (16). The medicine changes the lysosome's acidic environment, making it impossible for the cell to carry out endocytosis, exosome release, or phagolysosomal fusion in a systematic manner (17). Additionally, when chloroquine is present in the cytosol, it can interfere with the interaction of cytosolic DNA with the nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) (18). Chloroquine's interference causes the pH to rise in the lysosomes, which prevents the cell from presenting antigen, engaging in chemotaxis, or lysing proteins. Because autoantigenic peptides have a low affinity for self-MHC, the reduction in antigen presentation caused by the increase of pH by chloroquine leads to a reduction in the antigen-MHC complex. Other target cells' activity is inhibited as a result of the decreased self-peptide-MHC complex on antigen-presenting (AP) cells, and immune cells like T cells and other AP cells produce cytokines as a result (19). Additionally, several investigations shown that a number of human viruses, including influenza (20), Corona virus, which affects the respiratory system, enters cells with the aid of gangliosides connected to sialic acid (21). Researchers are looking into how

severe acute respiratory syndrome corona viruses enter human cells, specifically the sialic acid receptor (22), angiotensin converting enzyme receptor 2 (ACE2) (23), transmembrane serine protease 2 (TMPRSS2) (24,25), and extracellular matrix metalloproteinase inducer (CD147, also known as basigin) (26).

Human corona virus HCoV-O43 and orthomyxoviruses are inhibited by chloroquine through quinine reductase-2 inhibition of sialic acid production. The sialic acid moieties serve as receptors for the viruses (27), and chloroquine can hinder the efficient binding of spike protein to the host cell by reducing the glucosylation of ACE2.(28)

➢ *Pharmacokinetics of chloroquine:-*

After oral administration, chloroquine is broadly and gradually disseminated throughout the body as a result of widespread tissue sequestration, notably in the lung, liver, spleen, melanin-containing tissues, kidney, and to a lesser amount in the brain and spinal cord (29). The relatively low plasma half life of chloroquine is a result of its vast apparent volume of distribution. Numerous cell types store chloroquine. Studies on human Plasmodium falciparum cells and erythrocytes can be used to determine how chloroquine penetrates cells (30-32). The unprotonated form of chloroquine, which makes up a small portion of the extracellular chloroquine pool, is the major form of chloroquine that penetrates cells. However, a fraction of the residual chloroquine component dissociates to maintain equilibrium at the physiological pH because of the Henderson-Hasselbach equation. so that the medication may gradually reach the cells. The mechanism does not become saturated and the first intracellular accumulation of the medication is dose-dependent because passage across the plasma membrane is caused by diffusion rather than active transport. This pharmacokinetic characteristic enables the use of loading dosages to more quickly achieve the required intracellular concentrations. Again, in accordance with the Henderson-Hasselbach equation, chloroquine protonates at a rate that is inversely proportional to pH once it is within the cells (33). Chloroquine enters cells through the endosome, Golgi vesicles, and lysosomes, all of which have low pH levels and a high concentration of positively charged chloroquine molecules. (34)

➢ *Hypothesis : a case of SARS:-*

We put out the idea that chloroquine could be helpful in the clinical therapy of SARS based on its effects on a number of enveloped viruses and immunological activation. Ribavirin and oseltamivir, two well-known antiviral medications, have not yet proven effective in treating this condition (35). Recent research backs up the notion that coronaviridae replicate by using an endocytic route to infect their target cells (36,37)

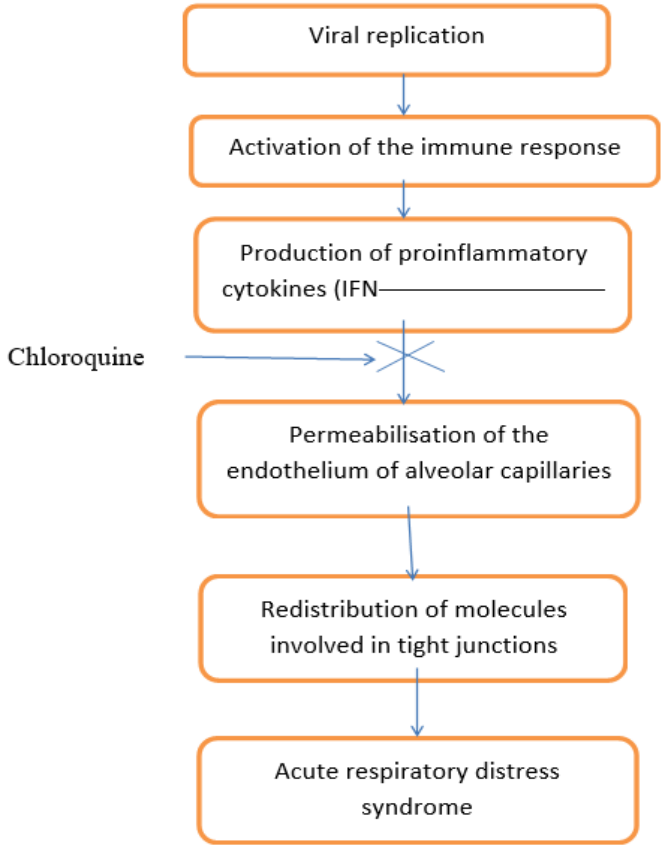

Fig 3 Mode of action of chloroquine

➢ *Antiviral activity of chloroquine:-*

Chloroquine is efficacious at both the entry and the post-entry stages of SARS-COV-2 infection in Vero E6 cells, according to an in vitro investigation (38). Chloroquine appears to be a versatile bioactive substance when tested in vitro. It has been reported to have antiviral activity against a variety of RNA viruses, including the rabies virus (39), hepatitis C virus (40), hepatitis A virus (41,42), HIV (43,44-46), poliovirus (47), Chikungunya virus (48-50), influenza A and B viruses (51-54), Zika virus (58), Dengue virus (56, 57), influenza A H5N1 virus (55), and other DNA viruses, including hepatitis B virus (59) and herpes simplex virus.

III. CONCLUSION

Regarding the effectiveness and potency of chloroquine for treating COVID-19, as well as proof of safety from long-term usage in clinical practice for other reasons, there is adequate pre-clinical knowledge, evidence, and data to detail clinical studies on the subject. Numerous coronaviruses have been demonstrated to be susceptible to chloroquine's ability to prevent their in vitro reproduction. The theory that chloroquine can enhance the clinical outcome of patients infected with SARS-CoV-2 is supported by recent publications. Although the binding of SARS-CoV to sialic acids has not yet been shown, chloroquine therapy will have an impact on this interaction if SARS-CoV-2, like other coronaviruses, targets sialic acids on

certain cell subtypes. Currently, preliminary results suggest that chloroquine inhibits cathepsins and interferes with SARS-attempts CoV-2's to acidify the lysosomes. We need a low pH for the best SARS-CoV-2 spike protein cleavage, which is necessary for the creation of the autophagosome. Additionally, chloroquine may disrupt the M protein's proteolytic processing and affect virion assembly and budding. Finally, this medication may indirectly treat COVID-19 illness by lowering the release of pro-inflammatory cytokines and/or by activating CD8+ T cells that are anti-SARS-CoV-2. Some of us highlighted the potential use of chloroquine to treat orphan viral infections in this publication as early as 2007. If the hopes sparked by chloroquine in the treatment of COVID-19 can be confirmed, it will be determined by the several ongoing trials throughout the world, including those involving the care of patients at our institute.

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