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Exhaustive Review of Studies in Silico Conducted in the Fight against COVID-19 that involved Hydroxychloroquine and/or Chloroquine alone, in Combination or Compared to other Therapeutic Agents

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Abstract: ***While the implementation of a SARS CoV2 vaccine is slow in coming. Several countries around the world are in the midst of a second wave of the COVID-19 pandemic. Current data shows considerable progress but also very questionable and sometimes contradictory results. Studies in silico optimize the time and cost of research. This exhaustive review on Pubmed, attempts to examine all the approaches in silico addressed since the start of fight against COVID 19, which have involved hydroxychloroquine and or chloroquine alone, combined or compared to other therapeutic agents such as antivirals. , phytochemicals and many more. Were used as targets, proteins involved in the pathways by which this virus enters host cell: Main protease COVID-19, receptor binding domain of SRAS-CoV-2 Spike protein, peak protein of SRAS -CoV-2 and envelope protein necessary in maturation processes of virus. . Other solutions to overcome challenges related to pharmacodynamic and pharmacokinetic properties of chloroquine and hydroxychloroquine were discussed. Well-tolerated and widely used drugs have also been selected for molecular dynamics simulations. The results will be reported in this review to allow future research to investigate new leads***

Keywords: Dynamic simulation, SRAS-CoV-2, Ligands, Covid-19

I. INTRODUCTION

In March 2020, governments around the world were warned of the potential consequences of a premature slackening of interventions. Studies have shown by modeling that the result of such decision could lead to an increase in contagiousness greater than 1.That is, a second wave of infection (Leung, Wu and al. 2020) . A situation we are living today. Pharmaceutical companies usually create drug programs around the concept: Unmet medical needs (for under-treated health problems).The main conditions of the Unmet Medical Need program are: -Disease with no existing or satisfactory treatment.

An urgent demand for effective therapy that is increasingly affecting patients. This concept is perfectly applicable to the current pandemic at COVID-19 . Determining an unmet medical need requires an understanding of the disease, available therapies, and possible gaps in treatment. Currently, potential strategies to control COVID-19 are summarized around antivirals, corticosteroids, convalescent plasma and vaccines. (Shamim, Khan and al. 2020). Several trials are in progress (Davis, Ferreira and al. 2020) , but several questions arise , in particular, the production of neutralizing or non-neutralizing antibodies, durability of immunity, reinfection and safety of new treatments. Within this context, in silico studies take a special place in the fight against COVID 19. These optimize the time and cost of research and offer new perspectives in development and repositioning of drugs. This exhaustive review attempts to examine all the in silico approaches that have been addressed since the beginning of the fight against COVID 19.

II. METHODS

On March 13, 2020, international science and technology advisers from a dozen countries, including the United States, called on publishers to voluntarily make their publications related to COVID-19 and coronavirus, as well as the available data supporting them, immediately available in PubMed Central (PMC) to support ongoing public health emergency response efforts (https://www.ncbi.nlm.nih.gov/pmc/about/covid-19/). Therefore, access to the full text of all publications was allowed. Given the new and recent nature of this pandemic at covid-19 . The search filter has been adjusted based on data available since the beginning of the pandemic (i.e. within the past year) and updated to October 31, 2020. Given the rapid development of the field and the accelerated diffusion of scientific discoveries concerning COVID-19 , more than 20,100 articles have been published. To meet our main objective, an exhaustive search was conducted on all in Silico studies conducted in the fight against COVID-19 that involved hydroxychloroquine and/or chloroquine alone, combined or compared to other therapeutic agents.

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The Pubmed survey was conducted for the SARS-CoV-2 studies using the following MeshData: Hydroxychloroquine and molecular docking and covid 19. The Pubmed database was consulted without language restriction . After reviewing the title and abstract 42 full-text studies were retrieved. 40 studies meeting the inclusion criteria were selected.

For identification of ligands studied, the databases Drug bank (https://go.drugbank.com/) and chemspider (http://www.chemspider.com/) were consulted. The Proteines Data Bank (pdb) (https://www.rcsb.org/) was consulted for the targets studied. The research on plants, chemicals, bioactivity and ethnobotany was based on Dr. Duke's current phytochemical and ethnobotanical data. (US Department of Agriculture, Agricultural Research Service. 1992-2016. Dr. Duke's phytochemical and ethnobotanical databases, https://phytochem.nal.usda.gov/). PubChem database was also consulted (https://pubchem.ncbi.nlm.nih.gov/).

III. RESULTS

In all the published studies in silico , the approaches were very different depending on the ligand and the target proposed in the molecular docking (Table 1).

Author/Year	Ligand	Targets	Interaction site
(Silva Arouche, Reis and al. 2020)	Remdesivir , ribavirin , favipiravir , galidesivir , hydroxychloroquine and chloroquine	The main COVID-19 protease (in complex with a COVID-19 N3 protease inhibitor)	The highest affinity values found in order from highest to lowest: Chloroquine , hydroxychloroquine , favipiravir , galidesivir , Remdesivir and ribavirin .
(Fantini, Chahinian and al. 2020)	Combined Therapy: Hydroxychloroquine (CLQ-OH) / Azithromycin (ATM)	Binding domain and site of attachment of the SARS-CoV-2 virus on gangliosides near the primary receptor of the virus, the angiotensin-2 converting enzyme (ACE-2).	MTA is directed against the virus while CLQ-OH is directed against cell attachment co-factors.
(Bailly and Vergoten 2020)	Natural Glycyrrhizic Acid (GLR)	At the membrane , the cholesterol of the lipid rafts that are important for the entry of the virus into the cell.	GLR a good candidate to be tested against Cov-2 SARS, alone and in combination with other drugs.
(Hagar, Ahmed and al. 2020)	Selected heterocyclic drugs: Favipiravir , amodiaquine , 2'-Fluoro-2'-deoxycytidine and ribavirin as an inhibitor and nucleotide analogues of COVID-19.	Main Protease of SRAS CoV-2 (PDB: 6LU7)	Amodiaquine has the lowest binding energy (-7.77 Kcal/mol) and could serve as a good inhibitor of SRAS CoV-2, remdisivir has a binding affinity of 4.96 Kcal/mol).
(Rajagopal, Varakumar and al. 2020)	Novel oxazine-substituted 9-anilinoacridines	Main protease of Sras CoV-2 (PDB: 5R82)	A38 has the highest G-score (-7.83) compared to all standard compounds proposed for the treatment of COVID-19 such as ritonavir (-7.48), nelfinavir (-5.93), lopinavir (-6.94), hydroxychloroquine (-5.47) and mataquine (-5.37).
(Nandi, Kumar and al. 2020)	34 drugs, including antivirals and antimalarials,	binding to COVID-19 proteases	13 compounds with good binding affinity were predicted to inhibit binding to COVID-19 proteases.
(Hamza, Ali and al. 2020)	Moringa oleifera, phytochemical leaf extracts (aqueous and ethanol) of flavonoids, anthraquinone and hydroxychloroquine.	Mass of amino acid sequences has been calculated and translated from the entire CoV2-SARS genome and identification of peptides that may be a target for inhibition.	Maximum energy obtained for hydroxychloroquine is -5.1 kcal/mol, kaempferol (flavonoid) is -6.2 kcal/mol and for anthraquinone -6 kcal/mol.
(Maiti and Banerjee 2020)	Tea flavonoids catechin products mainly epigallocatechin gallate or other such as theaflavin gallate and hydroxychloroquine (HCQ)	The central channel of the peak protein.	Tea flavonoids produced catechin products mainly epigallocatechin gallate or other such as theaflavin gallate have demonstrated a higher atomic contact energy (ACE) value, binding energy, Ki value, ligand efficiency, surface area and more amino acid interactions than hydroxychloroquine (HCQ) when bound.

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(Hathout, Abdelhamid and al. 2020)	Chloroquine CQ and Hydroxychloroquine HCQ	Angiotensin converting enzyme-2 (ACE-2) receptors, heparin sulfate proteoglycan and phosphatidylinositol-binding clathrin assembly protein (PICALM), which are expressed in lung and intranasal tissues and represent the initial sites of viral particles on the surface of respiratory cells.	Good binding of CQ and HCQ to these receptors
(Elfiky 2020)	sofosbuvir, ribavirine, galidesivir, remdesivir, favipiravir, céfuroxime, ténofovir, and Hydroxychloroquine	Viral protein-dependent RNA polymerase-RNA polymerase (RdRp) models built by docking and dynamics simulations	sofosbuvir, ribavirin, galidesivir, remdesivir, favipiravir, cefuroxime, tenofovir, and hydroxychloroquine, bind to SRAS-CoV-2 RdRp
(Khelfaoui, Harkati and al. 2020)	Eighteen drugs from the ACE2 Approved Drug Library that are structurally similar to chloroquine and hydroxychloroquine, the potential angiotensin-converting enzyme (ACE2) inhibitors	Two ACE2 receptors and the complex receptor [SARS-CoV-2 / ACE2] in two active sites	Ramipril , delapril and lisinopril , chloroquine and hydroxychloroquine bind to the ACE2 receptor and [SRAS-CoV-2 / ACE2] complex.
(Sehailia and Chemat 2020)	Artemisinin and its derivatives, hydroxychloroquine, arténimol	SRAS-CoV-2 Spike protein receptor binding domain	Further screening for artemisinin and derived compounds produced a better Vina docking score than hydroxychloroquine (-7.1 kcal mol -1 for artelinic acid versus -5.5 kcal mol -1 for hydroxychloroquine). Artesunate, artemisinin and artenimol showed two modes of interaction with the Spike protein binding hot spots Lys353 and Lys31.
(Ahmed, Abdelrheem and al. 2020)	caulerpine and its derivatives	Caulerpine and its derivatives as an adjunct to the SARS-CoV-2 receptor proteins: SRAS-CoV-2 Core Protease and SRAS-CoV-2 Spike Protein.	Molecular docking analysis showed that the binding energies of most of the caulerpine derivatives were higher than those of all the drugs suggested for both the
(Celı, Onay-Besı Kcı and al. 2020)	hydroxychloroquine and chloroquine	Crystalline structures of the SRAS-CoV-2 and ACE2 proteins	Hydroxychloroquine and chloroquine do not interact with the CoV-2-SRAS proteins, but bind to the amino acids ASP350, ASP382, ALA348, PHE40 and PHE390 at the allosteric ACE2 site rather than the active ACE2 site.
(Enmozhi, Raja and al. 2020)	Andrographolide of Andrographis paniculataen	Main protease of SRAS-VOC-2 (Mpro)	Andrographolide was successfully anchored in the SARS-CoV-2 Mpro binding site.
(Skariyachan, Gopal and al. 2020)	Chloroquine, Hydroxychloroquine, Favipiravir, Lopinavir, Remdesivir and Ritonavir)	15 potential targets for SRAS-CoV-2	Among the selected drugs, ritonavir and lopinavir showed improved binding to priority targets with minimal binding energy (kcal/mol), cluster-RMS, number of interacting residues and stabilizing forces relative to the binding of chloroquine, favipiravir and hydroxychloroquine
(Baildya, Ghosh and al. 2020)	Hydroxyxhloroquine	Main protease COVID-19	Snapshots of structural changes over time clearly indicate that the drug molecule has a profound impact on the binding sites as well as on the overall geometry of the protease moiety.
(Braz, Silveira and al. 2020)	Azythromycine (AZM) , Chloroquine (CQ) , and hydroxychloroquine (HCQ)	The main viral protease (M pro) and the cathepsin L host (CTSL) involved in the activation of the SARS-CoV-2 S peak protein and the receptor binding domain (RBD) of the SRAS-CoV-2 peak protein (S)	Results showed AZM affinity scores (ΔG) with strong interactions with ACE2, CTSL, M pro and RBD. CQ affinity scores showed three low energy (less negative) results with ACE2, CTSL and RBD. For HCQ, two results (ACE2 and M pro) were strongly related to receptors

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(Nimgampalle, Devanathan and al. 2020)	Chloroquine, l'hydroxychloroquine	SRAS-CoV-2 viral proteins.	Chloroquine and hydroxychloroquine can bind to specific structural and non-structural proteins involved in the pathogenesis of SRAS-CoV-2 infection with different efficiencies.
(Abdelrheem, Ahmed and al. 2020)	Caulerpine, chloroquine, hydroxychloroquine, azithromycin, remdesivir, baloxvir, lopinavir and favipiravir.	Main protease of CoV-SRAS-2-3CL (PDB ID: 6LU7) and the main proteases of CoV-SRAS (PDB ID: 2GTB and 3TNT)	Free energy binding between caulerpine and 6LU7 confirmed the efficacy of the caulerpine molecule against the main CoV-2-SRAS protease
(Deshpande, Tiwari and al. 2020)	Ritonavir, lopinavir, remdesivir, chloroquine, hydroxychloroquine (HCQ), routine antivirals such as oseltamivir and ribavirin. In addition, small molecules with anti-inflammatory actions such as mycophenolic acid (MPA), pemirolast, isoniazid and eriodictyol were also tested.	Proteins responsible for viral propagation, namely 3Clpro, Nsp10 / 16, Spike protein, SRAS protein receptor binding domain, single-stranded viral binding protein Nsp 9 and viral helicase The virus protein that penetrates the human angiotensin converting enzyme 2 (ACE2) receptor in the host cell is also used as a target for molecular anchoring.	The data generated confirm the potential of ritonavir, lopinavir and remdesivir as therapeutic candidates for SRAS-CoV-2. Eriodictyol is observed to bind to almost all selected target proteins with good binding energy, suggesting its importance in the treatment of COVID 19.
(Wang, Han and al. 2020)	Chloroquine (CQ) and Hydroxychloroquine (HCQ)	HEK293T high-expression ACE2 cells (ACE2 h cells)	Chloroquine (CQ) and Hydroxychloroquine (HCQ) show an equivalent suppression effect for the entry of the pseudotyped 2019-nCoV peak virus into ACE2 h cells.
(Beura and Chetti 2020)	Pharmacophore model (CQD15) of chloroquine and chloroquine derivatives	PDB_ID: 6LU7 Crystal structure of the main COVID-19 protease in complex with an N3 inhibitor	CQD15 which shows better interactions for the inhibition of SRAS-CoV-2 compared to chloroquine and hydroxychloroquine.
(Mukherjee, Dasgupta and al. 2020)	L'hydroxychloroquine (HCQ)	Viral genetic material is transcribed and replicated by the 3C protease. the main protease SRAS-CoV-2	A detailed structural overview of the presence of a water-mediated catalytic triad was obtained, which could be useful for inhibitor modeling.
(Chidambaram, Ali and al. 2020)	coumarin-based derivatives	The main protease of the SRAS coronavirus in complex with α-ketoamide (PDB ID: 5N5O)	the natural coumarin analogue, toddacoumaquinone, showed a remarkable inhibition capacity with a binding energy of -7.8 kcal/mol than other compounds against the main SRAS coronavirus protease in complex with α-ketoamide (PDB ID: 5N5O).
(Beck, Beck and al. 2020)	Hydroxychloroquine	CCR4: A G protein-coupled transmembrane receptor (GPCR) expressed throughout the human body with highest levels of expression in bone marrow and lymphoid tissue.	Such as improved survival rates due to a significant reduction in pro-inflammatory cytokine release and associated sepsis. These data suggest a potential role for the use of CCR4 antagonists in the treatment of COVID-19 patients.
(Gandhi, Rupareliya and al. 2020)	The phytoconstituents of the drugs: Nagaradi Kashaya which includes Sunthi (Zingiber officinalis Roscoe), Pushkarmool (Inula racemose Hook.F.), Guduchi (Tinospora cordifolia Miers.), Kantakari (Solanum virginianum L.) in comparison with hydroxychloroquine and quinine	SARS-CoV-2: An Ayurvedic perspective for SRAS-CoV-2-like symptoms with an in silico study	Binding energy and inhibition of Zingiber Officinalis (Sunthi) 6 gingesulfonic acid is superior to hydroxychloroquine and quinine

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(Achutha, Pushpa and al. 2020)	4-aminoquinoline and 8-aminoquinoline analogs of chloroquine.	Viral protease, called cysteine protease of the chymotrypsin type, also known as the main protease (3CL pro)	Six compounds provided better binding energies than chloroquine and hydroxychloroquine. Interactions with residues at the active site, particularly with Cys145 and His41, which are involved in the catalytic diad for proteolysis, make these compounds powerful inhibitors of the main protease
(Pandey, Rane and al. 2020)	10 potential natural phytochemical compounds (flavonoids / non-flavonoids) compared their affinity with hydroxychloroquine	The SRAS-CoV-2 lead protein	Fisetin, quercetin and kamferol bind to the hACE2-S complex with low free binding energy. The study provided an indication that these molecules may have the potential to disrupt the binding of the hACE2-S complex.
(Han, Wang and al. 2020)	Chloroquine, Hydroxychloroquine, Remdesivir, Ritonavir, Beclabuvir, Indinavir and Favipiravir) and a newly developed drug α-ketoamide (13b) inhibitor at the molecular level	3CL hydrolase (Mpro), indicating its ability to inhibit SRAS-CoV-2.	Chloroquine has the highest binding affinity for 3CL hydrolase (Mpro) among clinically approved drugs, indicating its effective inhibitory capacity for SRAS-CoV-2. However, the newly designed 13b inhibitor has potentially improved inhibition efficacy with higher binding energy compared to chloroquine.
(Gentile, Fuochi and al. 2020)	chloroquine (CQ) and hydroxychloroquine (HCQ)	Envelope protein (E), necessary in the maturation process of the virus,	CQ and HCQ have influenced the functionality of the envelope protein (E), which is necessary in the virus maturation processes, due to interactions that alter the flexibility of the protein structure. In addition, CQ and HCQ have also influenced viral RNA reuptake and capping in CoV-2-SRAS, achieved by nsp10 / nsp14 and nsp10 / nsp16. In particular, HCQ demonstrated better energy binding to the targets examined compared to CQ
(Ortega, Serrano and al. 2020)	Famotidine	Catalytic site of the three proteases associated with the replication of SRAS-CoV2.	Famotidine could interact in the catalytic site of the three proteases associated with the replication of SRAS-CoV2. However, the low binding affinity of famotidine to these proteases suggests that successful famotidine therapy could probably only be achieved in combination with other antiviral drugs.
(Dave, Rakholiya and al. 2020)	Total of 30 compounds of Solanum tuberosum and Brassica juncea flue water residues	SRAS-CoV-1, SARS-CoV-2 and cellular proteins involved in the mechanism of infection.	Docking analysis identified lead molecules with favorable binding energy, pose number and hydrogen bonding interactions, indicating efficient modulation of ACE2 and TMPRSS2 receptors.
(Belhassan, En-Nahli and al. 2020)	eighteen imidazole derivatives based on 7-chloro-4-aminoquinoline	Main protease of SARS-CoV-2.	Molecules Nos. 3, 7 and 14 have higher binding energy to the newly crystallized CoV-2-SRAS core protease (bp code 6LU7) compared to other imidazole derivatives and the two drugs; chloroquine and hydroxychloroquine.
(Basu, Veeraraghavan and al. 2020)	Using curcumin as the reference compound,a commercially available cyclohexanone compound, ZINC07333416 versus Lopinavir, the nucleoside analogue Remdesivir and the reused drug hydroxychloroquine	Actif site of the SRAS-CoV-2 main protease (Mpro)	ZINC07333416 with better binding energy (-8.72 kcal/mol) than the commonly designed anti-Covid-19 drugs such as the viral protease inhibitor Lopinavir, the nucleoside analogue Remdesivir and the reused drug hydroxychloroquine .

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(Tiwari 2020)	VTAR-01 designed by novo based on fragments of selected molecules, namely ascorbate, ribavirin, lopinavir, and hydroxychloroquine.	RBD-hACE2 interaction interface	Ribavirin, ascorbate, lopinavir and hydroxychloroquine have a strong interaction at the RBD-hACE2 interface.
(Gul, Ozcan and al. 2020)	Tetracycline, dihydroergotamine, ergotamine, dutasteride, nelfinavir and paliperidone, eltrombopag, tipranavir, ergotamine and conivaptan, dihydroergotamine, bromocriptine, dutasteride, conivaptan, paliperidone and tipranavir.	SRAS-CoV-2 3C protease (3CL pro) and viral RNA-dependent RNA polymerase (RdRp)	Tetracycline, dihydroergotamine, ergotamine, dutasteride, nelfinavir and paliperidone formed stable interactions with 3CL pro eltrombopag, tipranavir, ergotamine and conivaptan bound to the enzyme with high free binding energies. Mooring results suggest that ergotamine, dihydroergotamine, bromocriptine, dutasteride, conivaptan, paliperidone and tipranavir can bind to both enzymes with high affinity.
(Kumar, Kashyap and al. 2020)	Phytochemical compounds such as sarsasapogenin, ursonic acid, curcumin, ajmalicin, novobiocin, silymarin and aranotine, piperine, gingerol, rosmarinic acid and alpha terpinyl acetate. Hydroxychloroquine is used as a positive control, as well as nelfinavir.	Nsp15 protein was selected because it has an 89% similarity with the other SRAS-CoV, which caused the previous epidemic. The hypothesis is that inhibition of SP15 inhibits viral replication.	Phytochemicals such as sarsasapogenin, ursonic acid, curcumin, ajmalicin, novobiocin, silymarin and aranotine, piperine, gingerol, rosmarinic acid and alpha terpinyl acetate to viral protein against SP15 could play a key role in inhibiting the replication of CoV-2-SRAS
(Abdelli, Hassani and al. 2020)	Natural compounds (Isothymol, Thymol, Limonene, P-cymene and γ-terpinene) derived from the essential oil of the antiviral and antimicrobial plant Ammoides verticillata	Angiotensin converting enzyme 2 (ACE2) as a SRAS-CoV-2 receptor	Isothymol gives the best docking scores compared to the co-crystallized β-D-mannose inhibitor of the ACE2 enzyme, the drug Captropil as a good inhibitor of ACE2 and the antiviral drug Chloroquine also involved in other mechanisms such as the inhibition of the ACE2 cell receptor

IV. DISCUSSION

Several critical reviews (Singh, Singh and al. 2020) , systematic reviews (Antonio, Wiedemann and al. 2020) , and pharmacological (Singh, Parida and al. 2020) have been published on different treatments or trials used in the fight against COVID-19. No exhaustive and exclusive review o studies in silico of hydroxychloroquine and or chloroquine alone, combined or compared with other therapeutic agents has been conducted. For the first time we propose to discuss the recent results obtained by molecular docking of ligands identified as potentials in different works with several targets involved in penetration, replication and transmission of COVID-19 infection.

To date, more than 30 peer-reviewed articles published on Medline have reported the results of molecular docking of hydroxychloroquine and chloroquine alone, in combination or as positive controls for SARS CoV2-19 (Table 1).

Baildya and al concluded that hydroxyxhloroquine confers good inhibitory response to the main protease COVID-19 (Baildya, Ghosh and al. 2020) . However, prolongation of the QT interval in patients taking hydroxychloroquine with azithromycin, a combination that has proven effective in European clinical trials, raised concerns about the use of these drugs in the treatment of COVID-19 (Mazzanti and al., 2020). Beck and al's study identified CCR4 (Transmembrane receptor,(GPCR) expressed at high levels in bone marrow and lymphoid tissue) as immunomodulatory target of hydroxychloroquine. Authors propose to substitute the latter with CCR4 antagonists that do not promote prolongation of QT interval, such as the FDA-approved drug mogamulizumab or investigational compound K777 for the treatment of severe coronavirus disease as monotherapy or in combination with antivirals (Beck, Beck and al. 2020) . Nimgampalle and al demonstrated that chloroquine and hydroxychloroquine can bind to specific structural and non-structural proteins involved in pathogenesis of SRAS-CoV-2 infection with different effectiveness (Nimgampalle, Devanathan and al. 2020) . These results corrhoborate with those of Wang and al on HEK 293T cells with high ACE2 expression (ACE2 h cells) (Wang, Han and al. 2020). Results of Gentile and al showed that CQ and HCQ influenced the functionality of envelope protein (E), necessary in the virus maturation processes, due to interactions that alter flexibility of the protein structure.

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In addition, Chloroquine and HCQ also influenced rereading and capping of viral RNA in SRAS-CoV-2, made by nsp10 / nsp14 and nsp10 / nsp16. In particular, Hydrxychloroquine demonstrated better energetic binding with targets examined compared to Chloroquine (Gentile, Fuochi and al. 2020). Achutha and al demonstrated efficacy of four 4-aminoquinoline and 8-aminoquinoline analogues of chloroquine showing resemblance to SARS-CoV-2 (Achutha, Pushpa and al. 2020). Beura and Chetti showed that pharmacophore model (CQD15) of chloroquine and chloroquine derivatives have better interactions for inhibition of SRAS-CoV-2 than the latter two (Beura and Chetti 2020). Main viral protease (M pro) and host cathepsin L (CTSL) are part of proteolytic systems involved in the activation of the SRAS-CoV-2 S protein and receptor binding domain (RBD) of the SRAS-CoV-2 (S) peak protein . Braz and al showed that azithromycin had strong interactions with ACE2, CTSL, M pro and RBD. Chloroquine affinity scores showed three low energy (less negative) results with ACE2, CTSL and RBD. For Hydroxychloroquine , two results (ACE2 and M pro) were strongly related to receptors (Braz, Silveira and al. 2020). Combined hydroxychloroquine / azithromycin therapy, proposed in silico by Fantini and al had synergistic beneficial effects in patients with COVID-19 (Fantini, Chahinian and al. 2020).

These results are contradictory with those of Fiolet and al. Systematic review and meta-analysis was conducted by authors to evaluate effect of hydroxychloroquine with or without azithromycin on mortality in patients with COVID-19 . Hydroxychloroquine alone was not associated with reduced mortality in hospitalized patients with COVID-19, but combination of hydroxychloroquine and azithromycin significantly increased mortality. (Fiolet, Guihur and al. 2020).

Other anti-malarial drugs have also been tested. (Nandi, Kumar and al. 2020). For artemisinin and its derivatives, by taking as target the receptor binding domain of the SRAS-CoV-2 Spike protein. Sehailia and Chemat noted that hydroxychloroquine could act as good inhibitor but artemisinin and derived compounds had better Vina docking score (better affinity). In view of an excellent history of safety in humans against various conditions, authors requested a protocol for extracting artemisinin from Artemisia annua. (Sehailia and Chemat 2020) . Critical review of pharmacology, preclinical and clinical studies was performed by Singh, Singh and al on Remdesivir in COVID-19. According to authors, initial compassionate use of remdesivir showed fairly good result, but difficult to quantify, in the absence of a control arm. While the very first randomized, double-blind, placebo-controlled trial conducted in Wuhan found no significant advantage over the control, the preliminary result of another similar multi-center trial showed faster recovery time but no difference in mortality . (Singh, Singh and al. 2020)

Concerning in silico experimentations. In the study of Silva Arouche, Reis and al which included as ligands remdesivir, ribavirin, favipiravir, galidesivir, hydroxychloroquine and chloroquine. affinity energy values obtained for hydroxychloroquine ligands were -9.9 kcal/mol and for chloroquine -10. 8 kcal/mol indicating that the coupling contributes to an effective improvement in affinity energies with the main protease of COVID-19 in complex with a COVID-19 N3 protease inhibitor (Silva Arouche, Reis and al. 2020).

Results of docking eight other almost similar compounds (sofosbuvir, ribavirin, galidesivir, remdesivir, favipiravir, cefuroxime, tenofovir, and Hydroxychloroquine) with viral protein-dependent RNA polymerase RNA (RdRp) models constructed by dynamic simulations showed mean binding affinities for all drugs in the same range (-6.13 (Hydroxychloroquine) and up to -7.46 (Sofosbuvir) kcal/mol) (Elfiky 2020). In addition, remdesvir tested against fifteen potential SRAS-CoV-2 targets showed better binding to priority targets compared to binding of chloroquine, favipiravir and hydroxychloroquine, but showed lower binding potential compared to interaction between ritonavir and lopinavir (Skariyachan, Gopal and al. 2020) . Hagar and al have selected certain heterocyclic drugs (Favipiravir , Amodiaquine , 2'-Fluoro-2'-deoxycytidine and Ribavirin) evaluated as inhibitors and nucleotide analogues of COVID-19. Docked to the main protease SRAS-CoV-2 (PDB: 6LU7), hydroxychloroquine had low binding affinity compared to amodiaquine: -6.06 Kcal/mol (Hagar, Ahmed and al. 2020) . In same perspective, molecular docking and molecular dynamics were performed for two ACE2 receptors and complex receptor [SARS-CoV-2 / ACE2] in two active sites to find ligand, which can inhibit COVID-19. Of the eighteen drugs, which are similar structure to chloroquine and hydroxychloroquine, potential angiotensin converting enzyme (ACE2) inhibitors , Ramipril, delapril and lisinopril had shown good binding to ACE2 receptor and [SARS-CoV-2 / ACE2] complex than chloroquine and hydroxychloroquine(Khelfaoui, Harkati and al. 2020). Ritonavir, lopinavir, remdesivir, chloroquine, hydroxychloroquine (HCQ), routine antivirals such as oseltamivir and ribavirin molecules with anti-inflammatory actions such as mycophenolic acid , pemirolast, isoniazid and eriodictyol were also tested against proteins responsible for viral propagation (3Clpro, Nsp10/16, Spike protein, SRAS protein receptor binding domain, single-stranded viral binding protein Nsp 9 and viral helicase). Molecular interactions of ritonavir, lopinavir and remdesivir against SRAS-CoV-2 proteins have enhanced their potential as drug candidate for treatment of COVID-19. (Deshpande, Tiwari and al. 2020) . Ahmed and al tested caulerpin and its derivatives as an adjunct drug against SARS-CoV-2 receptor proteins: Main protease SARS-CoV-2 and peak protein of SRAS-CoV-2.

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In combination with lopinavir, simeprevir, hydroxychloroquine, chloroquine and amprenavir, caulerpine could be used to disrupt stability of SRAS-CoV2 receptor proteins, to increase antiviral activity (Ahmed, Abdelrheem and al. 2020). Free energy binding between caulerpine and main protease of SRAS-CoV-2-3CL (6LU7) confirmed efficacy of caulerpine molecule (Abdelrheem, Ahmed and al. 2020).

Other phytochemical, natural, flavonoid and non-flavonoid products have demonstrated their effectiveness in silico. Review by Antonio and al aimed to systematically evaluate natural metabolites that could potentially be used against this new disease by looking at their natural sources, mechanism of action and previous pharmacological uses (Antonio, Wiedemann and al. 2020)

However, important questions still need to be addressed regarding in vivo bioavailability and efficacy. In our review we have selected, on Medline, only those that have been tested in silico since the beginning of COVID-19 pandemic Study by Kumar and al successfully demonstrated binding of phytochemical compounds such as sarsasapogenin, ursonic acid, curcumin, ajmalicin, novobiocin, silymarin and aranotine, piperine, gingerol, rosmarinic acid and alpha terpinyl acetate to viral protein Nsp15 and could play key role in inhibiting replication of SRAS CoV-2. Hydroxychloroquine was used as positive control (Kumar, Kashyap and al. 2020) . Tea flavonoids (epigallocatechin gallate and theaflavin gallate) demonstrated higher atomic contact energy (ACE) value, binding energy, Ki value, ligand efficiency, surface area and more amino acid interactions than hydroxychloroquine when binding in central channel of the peak protein . These flavonoids bound to three distinct binding sites (I, II, and III) of spike nucleus when HCQ binds only at site III (the site furthest from the nCoV-RBD contact of ACE2) (Maiti and Banerjee 2020). Gandhi and al have hypothesized to use Nagaradi Kashaya which includes Sunthi (Zingiber officinalis Roscoe), Pushkarmool (Inula racemose Hook.F.), Guduchi (Tinospora cordifolia Miers.) , Kantakari (Solanum virginianum L. Binding energy and inhibition of 6 gingesulfonic acid of Zingiber Officinalis (Sunthi) was higher than hydroxychloroquine and quinine (Gandhi, Rupareliya and al. 2020). A total of 30 compounds of Solanum tuberosum and Brassica juncea smoke water residues were tested. Docking analysis indicated (a) curcumenol, (b) N-desmethylselegiline, (c) phentermine and (d) sphingolipid derivatives as selective and potent candidates over hydroxychloroquine for treatment with COVID- 19(Dave, Rakholiya and al. 2020) . Using curcumin as reference compound, Basu and al identified new commercially available cyclohexanone compound, ZINC07333416 Versus Lopinavir, the nucleoside analogue Remdesivir and the reused drug hydroxychloroquine. . ZINC07333416 with better binding energy (-8.72 kcal/mol) than commonly designed anti-Covid-19 drugs such as viral protease inhibitor Lopinavir, the nucleoside analog Remdesivir and the reused drug hydroxychloroquine when targeted to active site of main protein SRAS-CoV-2 (Mpro) (Basu, Veeraraghavan and al. 2020) . Angiotensin Converting Enzyme 2 (ACE2) as a SARS-CoV-2 receptor, a potential therapeutic target for COVID -19 virus has been docked to natural compounds (Isothymol, Thymol, Limonene, P-cymene and γ-terpinene) derived from essential oil of antiviral and antimicrobial plant Ammoides verticillata . Isothymol, a major component of this plant, gives best docking scores compared to co-crystallized β-D-mannose inhibitor of ACE2 enzyme, Captropil as a good inhibitor of ACE2 and Chloroquine also involved in other mechanisms such as inhibition of ACE2 cell receptor . (Abdelli, Hassani and al. 2020) .

Andrographolide from Andrographis paniculataen has been used because chloroquine and hydroxychloroquine derivatives are not suitable for patients with conditions such as diabetes, hypertension and heart problems. Andrographolide was successfully docked in binding site of SRAS-CoV-2 Mpro . (Enmozhi, Raja and al. 2020) . Other leads have been investigated:

Some new oxazine-substituted 9-anilinoacridines have been identified by molecular docking as significantly active inhibitors against the main protease of SRAS-CoV-2 compared to hydroxychloroquine (Rajagopal, Varakumar and al. 2020)

VTAR-01 was developed by new method on selected molecular fragments, namely ascorbate, ribavirin, lopinavir and hydroxychloroquine. This hybrid molecule provided better interaction with RBD-hACE2 interface than any antiviral drug used to design it (Tiwari 2020). In another approach, natural coumarin analog, toddacoumaquinone, showed remarkable inhibition capacity with binding energy of -7.8 kcal/mol than other compounds against main protease SRAS coronavirus in complex with α-ketoamide (PDB ID: 5N5O) (Chidambaram, Ali and al. 2020) .

Currently, there is no safe and effective therapy option for COVID-19 . The reuse approach is seen as the best alternative since it involves less time and cost to find new therapeutic agent. Singh and al reviewed mechanism of action, pharmacokinetics, and tolerability of these already approved drugs (Singh, Parida and al. 2020). In Drug Design, in silico studies that use these molecules are therefore taking big step towards the fight against COVID-19 Well-tolerated and widely used drugs have been selected for molecular dynamics simulations with SRAS-CoV-2 3C protease (3CL pro) and viral RNA-dependent RNA polymerase (RdRp).

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Tetracycline, dihydroergotamine, ergotamine, dutasteride, nelfinavir and paliperidone formed stable interactions with 3CL pro . Eltrombopag, tipranavir, ergotamine, and conivaptan bound to enzyme with high free binding energies. Docking results suggest that ergotamine, dihydroergotamine, bromocriptine, dutasteride, conivaptan, paliperidone and tipranavir can bind to both enzymes with high affinity(Gul, Ozcan and al. 2020). Famotidine could also interact in catalytic site of the three proteases associated with SRAS-CoV2 replication. Pharmacokinetic parameters indicated that its effect against SRASS-CoV2 infection could only be achieved by intravenous administration (Ortega, Serrano and al. 2020). This prospect of reuse is very broad given available drugs that may be candidates against SRAS-CoV2.

V. CONCLUSION

All identified studies in silico tested hydroxychloroquine and/or chloroquine alone, in combination or compared to other therapeutic agents docked to different targets of COVID-19 virus but not to other collateral targets. It is true that pharmacology of drugs repositioned in fight against COVID-19 is known and approved but the uncertainty surrounding this new virus highlights contradictory debate in scientific community. It would be reasonable to reconsider hopes based on discovery of new drugs for induction of reliable immunity (neutralizing antibodies) and lasting over time. In this context, studies in silico should be continued for better understanding of COVID-19 infection.

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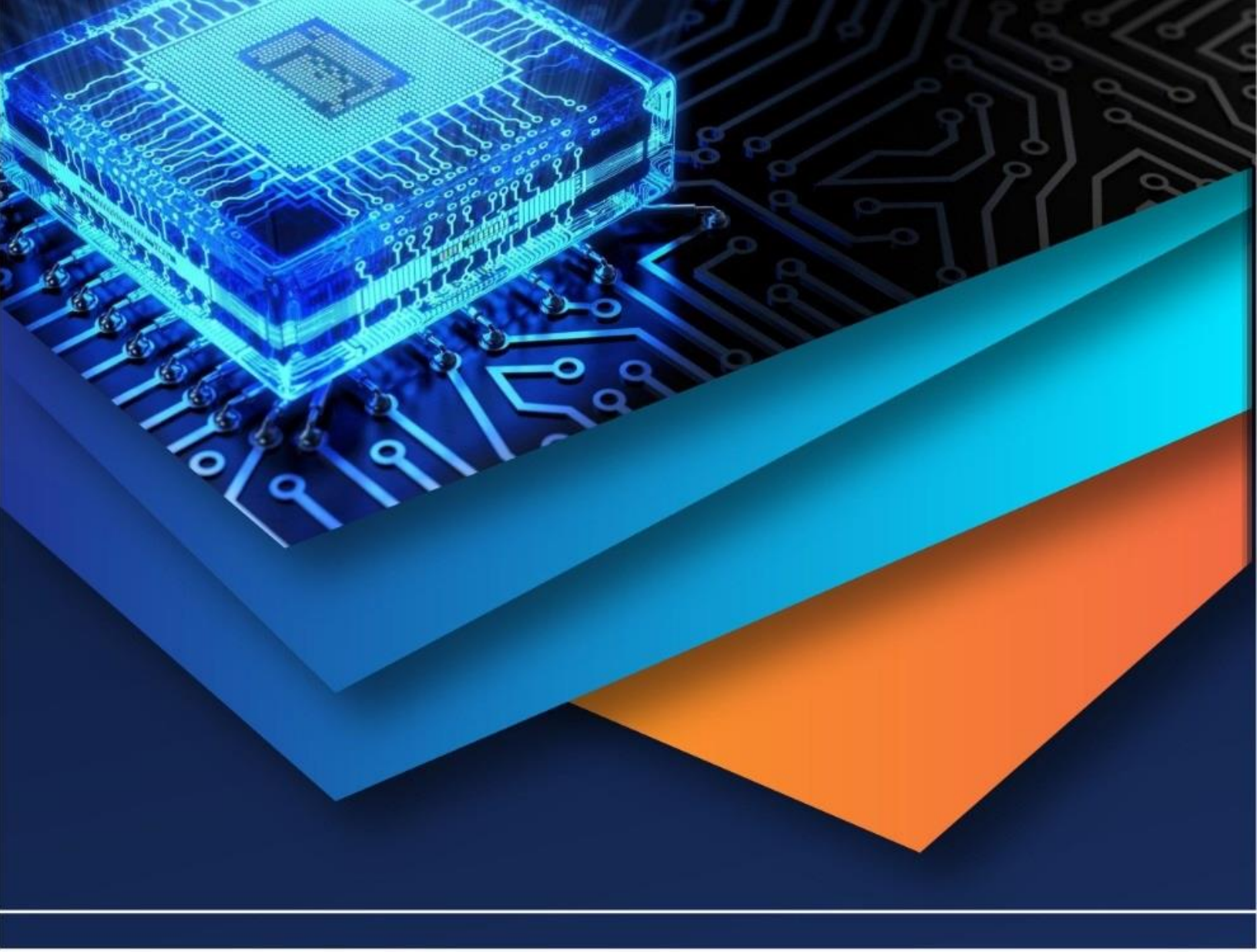

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