Caliphate Medical Journal

A Publication of Nigerian Medical Association Sokoto State Chapter.

Vol 9, No. 4, October - December, 2021

ISSN: 2346-7193

In this Issue

CMJ

Also available @ www.cmj.nmasokoto.org

CHLOROQUINE A POTENTIAL DRUG CANDIDATE FOR THE MANAGEMENT OF SNAKE BITE: A STRUCTURE BASED VIRTUAL SCREENING FOR MULTI-TARGET PROFILING

Yunusa A, Adamu HI, Chika A, Jimoh AO, Tukur UM, Adamu AA, Zauru RA, Aluefua OF, Bello SO

Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University Sokoto, Nigeria.

ABSTRACT

Background: Considering the diversity in the pharmacological actions of chloroquine, it is likely that other potential mechanisms may exist in its action against other targets. Anti-snake-venom treatment is very expensive, out of reach and have several adverse effects because of the foreign protein involved, hence need for a cheaper, safer, readily available and more effective drug.

Materials and Methods: PASS ONLINE target identification, molecular docking and pharmacophore modelling approach were employed in the structure based virtual screening against multiple snake venom proteins.

Results: Six (6) snake venom proteins were selected from the PASS online screening software as potential targets for chloroquine; snake acetylcholinesterase, snake venom cardiotoxin, interferon 2A, tumor necrosis factor alpha, snake hemorrhagic metalloproteinase and snake phosphodiesterases. Chloroquine demonstrated excellent binding affinities (when compared to the co-crystallized ligands) against the six snake venom proteins. Additionally, it fits into the active pockets of the six targets. Again, chloroquine interacts with the amino acid residues of the snake venom proteins at its pharmacophore site. These findings showed the ability of chloroquine to effectively bind to these targets thereby inhibiting their effects.

Conclusion: Though several studies have attempted to repurpose chloroquine for other indications. This study was the first to predict the activity of chloroquine against snake venom targets.

Keywords: Chloroquine, molecular docking, Pharmacophore, snake venom proteins

Corresponding Author's:

Yunusa Abdulmajeed,

Department of Pharmacology and Therapeutics,
Faculty of Basic Clinical Sciences,
College of Health Sciences,
Usmanu Danfodiyo University Sokoto, Nigeria.
Email: abdulmajeedyunusa@gmail.com

Introduction

Chloroquine (CHQ) was first synthesized in Germany by Bayer Corporation in 1934 as a cheaper alternative to the costly naturally occurring quinine, but was then considered toxic for any significant biological use.^{1,2} However, as the demand for cheaper, readily available antimalarial drugs escalated during World War II, thousands of compounds were synthesized and tested for activity, Chloroquine eventually proved most promising and was released for field trial. It received a new lease of life and was subsequently discovered to be more effective than the costly quinine or quinidine against intra-erythrocytic malarial parasites.¹ For the following two decades thereafter (1946-1966), CHQ emerged as the drug of choice for treatment and prophylaxis of malaria in most disease endemic tropical countries.³ Subsequently the drug was approved for several other clinical indications due to their diverse pharmacological effects. It is commonly sold as an over-the-counter medication and is also used as an anti-inflammatory drug in the treatment of rheumatoid arthritis, discoid lupus erythematosus and amoebic hepatitis.⁴ CHQ inhibits pro-inflammatory cytokine release into human whole blood and may be of therapeutic benefit not only during chronic inflammation, but also in diseases that are related to bacteria-induced inflammation.

In 2009, WHO listed snakebite as a neglected tropical disease, recognizing its importance alongside many infectious diseases affecting millions of people in tropical and subtropical areas of the world.⁵ Snakebite has remained an enduring problem for many decades and little progress has been made in reducing morbidity and mortality.^{5,6} There are number of reports describing the poor performance and failure of anti-venoms at neutralizing venom from snakes.⁷ Recent reports suggested that certain anti-venoms might have greater para-specificity than previously anticipated.⁸ Anti-venom treatment is very expensive, out of reach and have several adverse effects

because of the foreign protein involved, hence need for a cheaper drug with lesser side effect and readily available. Unfortunately, access to these vital drugs is limited, principally due to their cost.⁶ Around 70% of the immunoglobulins obtained do not act directly against venom toxins.⁶ Despite the above-mentioned facts, this is the only FDA approved therapy to treat snake venom.

Considering the diversity in the pharmacological actions of chloroquine, it is likely that other potential mechanisms may exist in its action against other targets. This study was therefore aimed at evaluating chloroquine against multi-snake venom proteins using structure based virtual screening approach.

Methodology

Virtual Screening of Chloroquine against Six (6) Selected Targets Using Pyrx Virtual Screening Tool Using PASS Online tool to predict other indications for chloroquine

PASS (Prediction of Activity Spectra for Substances) online software was used to select six (6) snake venom protein targets. Briefly, the 3D structure of chloroquine was uploaded into the query space of the software and a 'run' tab was clicked. An automated algorithm was generated by the software which was used to predict several biological targets.⁹

Development of Local Database of Protein Targets from Protein Data Bank

Protein Data Bank (PDB) is an archive of 3D structures of about 35,000-50,000 biological molecules. Six (6) important snake venom protein targets; which include acetylcholinesterase, metalloproteinase, snake venom cardiotoxin, TNF, interferon, and interleukin (in PDB text format) were selected and downloaded from the PDB website (www.rcsb.org) and saved in PDB text format. A local database was created for the viral targets in my personal computer (Smart *et al.*, 2018). Briefly, The PDB ID of the macromolecule was typed in the search space of Protein

Data Bank. The 3D structure of the macromolecule appeared in the left upper hand corner of the data bank. Then the “Download files” tool was selected displaying different downloading options and formats, and Pdb-gz format was selected since PyRx recognizes this format. This displayed the “opening pdb-gz box” with the option “to save”. The macromolecules were saved in a computer local Database.¹⁰

Development of Local Database for Chloroquine from DrugBank

A Drug Bank is a drug Database that contains more than 4,000 compounds linked to about 14,000 molecular targets. Chloroquine was downloaded from DrugBank website (www.drugbank.ca) and saved in structural data format (SDF).¹¹

Importation of Macromolecules from the Local Database

To import macromolecule from local Database, File > Import molecule was selected, this displayed “import molecule wizard” carrying different options. Workspace Tarball > local File was then selected and “Next” button clicked followed by Finish button. Shortly an “Import Completed Successfully” dialog appeared; then OK button was clicked. The 3D structure of the macromolecule was displayed in the workspace and the protein ID appeared in the “molecule tab” of the navigator panel. Atoms of the macromolecule were viewed in the workspace by deselecting and selecting them in the “molecule tab” of the navigator panel. The macromolecule was inspected in the workspace by right clicking and holding the mouse. The binding site of the co-crystallized area examined, in shape, size, polarity and accessibility. The molecule can be toggle across different axis using the “view axis” in the “view panel” of the 3D scene and the full screen displayed using “display full screen” in the “view panel” of the 3D scene.¹²

Importation of Ligands from the Local Database

To import ligands from the local Database, 'open babel' button was selected in the control panel of the PyRx tool. The 'insert new item' tab on the upper left-hand corner of the open babel panel was selected and a “choose open babel supported file” box appeared. The ligand of interest was then selected and imported into the PyRx. The selected ligands appeared in the 'open babel results table' displaying the drugs ID, formula, weight and Log P. Minimized atomic coordinates of the ligand was created using “the minimize all” widget. The minimized coordinate of the ligands right clicked and different options displayed. The option “Covert all to autodock ligand PDBQT” was selected. The PDBQT format of the ligand appeared in the ligand compartment of the autodock navigator area.¹²

Preparation of Ligands and Macromolecules

The molecule ID in the molecule tab of the navigator area was selected and right clicked, then “autodock” > “make macromolecule” selected. Shortly the macromolecule appeared in the macromolecule compartment of the autodock navigator panel. Here the molecule appeared in the PDBQT format, a format recognized by the PyRx virtual screening tool. Again, the molecule ID in the molecule tab of the navigator area was selected and right clicked, then “autodock” > “make ligand” selected. Shortly the ligand appeared in the ligand compartment of the autodock navigator panel.¹²

Running an autodock/vina wizard includes “Start here”, “Select molecule”, Run vina/autodock, and “Analyze results”. The “Start here” button was clicked to activate the autodock vina mode. The ligands of interest were selected from the autodock widget and “select ligand” button pressed, followed by the forward button. The ligands were automatically imputed into the ligand list in the control panel of PyRx software. Again, the macromolecules were selected from the autodock widget and “select macromolecule” button pressed followed by the 'forward' button and this automatically input macromolecules into the macromolecule list in the control panel.

To run vina, the “run vina” was clicked, then forward button pressed. Finally, “analyze result” was selected then 'forward' button. This displayed the binding affinities of the various poses against the ligands. The lower the binding affinities the better the protein-ligand interaction, since molecules interact to conserve energy.¹³

Analysis of Results

The Analyze results page is where the final docking results were presented. The table was sorted according to the values of the binding energies. The table row was selected one by one to see the corresponding docking pose for each ligand-protein complex in the 3D scene. The numerical results were exported as a Comma-Separated Values (CSV) file compatible with excel.¹³

Results

Passonline Prediction of Chloroquine Targets

Sixty-six (66) targets were predicted as potential molecular targets for chloroquine. Six (6) of the targets (snake acetylcholinesterase, snake venom cardiotoxin, interferon 2A, tumor necrosis factor alpha, acutolysin, and snake phosphodiesterases) were snake venom proteins. These six targets were selected for virtual screening simulations, see tables 1 & 2.

Table 1: Passonline Results for Chloroquine

S/N	Predicted Chloroquine Targets
1.	Taurine dehydrogenase inhibitor
2.	Fructose 5-dehydrogenase inhibitor
3.	Gluconate 2-dehydrogenase (acceptor) inhibitor
4.	2-Hydroxyquinoline 8-monooxygenase inhibitor
5.	Amine dehydrogenase inhibitor
6.	Nicotinate dehydrogenase inhibitor
7.	4-Hydroxyproline epimerase inhibitor
8.	Nitrate reductase (cytochrome) inhibitor
9.	Spermidine dehydrogenase inhibitor
10.	Sulfur reductase inhibitor
11.	Nicotine dehydrogenase inhibitor
12.	Antiprotozoal (Plasmodium)
13.	Hydroxylamine reductase inhibitor
14.	(R)-Pantolactone dehydrogenase (flavin) inhibitor
15.	4-Hydroxymandelate oxidase inhibitor
16.	Retinal dehydrogenase inhibitor
17.	Benzoate 4-monooxygenase inhibitor
18.	Aldehyde oxidase inhibitor
19.	Glycosylphosphatidylinositol phospholipase D inhibitor
20.	4-Methoxybenzoate monooxygenase (O-demethylating)

Running the Molecular Docking Simulation

S/N	Predicted Chloroquine Targets
	inhibitor
21.	Nitrite reductase [NAD(P)H] inhibitor
22.	Cyclohexanone monooxygenase inhibitor
23.	Malate dehydrogenase (acceptor) inhibitor
24.	Antiprotozoal (Amoeba)
25.	Acetylsermidine deacetylase inhibitor
26.	Rubredoxin-NAD ⁺ reductase inhibitor
27.	Antiprotozoal (Leishmania)
28.	Membrane integrity antagonist
29.	Antiprotozoal
30.	Glycerol-3-phosphate oxidase inhibitor
31.	Cytochrome-b5 reductase inhibitor
32.	Ethanolamine oxidase inhibitor
33.	Acidifying agent non gastric
34.	Spasmolytic, urinary
35.	CYP2D6 substrate
36.	CYP2C8 inhibitor
37.	CYP2D substrate
38.	Polyamine oxidase inhibitor
39.	Gamma-butyrobetaine dioxygenase inhibitor
40.	L-amino-acid oxidase inhibitor
41.	Pseudolysin inhibitor
42.	Hydroxylamine oxidase inhibitor
43.	Phthalate 4,5-dioxygenase inhibitor
44.	Botulin neurotoxin A light chain inhibitor
45.	Skeletal muscle relaxant
46.	Antialcoholic
47.	Loop diuretic
48.	Prion diseases treatment
49.	Fibrolase inhibitor
50.	Antiprotozoal (Trichomonas)
51.	Antituberculosic
52.	Antiseborrheic
53.	Acetylcholine neuromuscular blocking agent
54.	Venom exonuclease inhibitor
55.	5-O-(4-coumaroyl)-D-quinatate 3'-monooxygenase inhibitor
56.	Ribitol 2-dehydrogenase inhibitor
57.	Bacterial efflux pump inhibitor
58.	Telomerase inhibitor
59.	Interleukin 2 antagonist
60.	Cyclic AMP phosphodiesterase inhibitor
61.	Methionyl aminopeptidase inhibitor
62.	Indoleacetaldoxime dehydratase inhibitor
63.	Trimethylamine-oxide aldolase inhibitor
64.	Interferon agonist
65.	TNF expression inhibitor
66.	Protein kinase (CK2) inhibitor

Docking Results of the Snake Venom Proteins Against Chloroquine and the Co Crystallized Ligands

Chloroquine had excellent binding affinities against the six snake venom proteins better than the co-crystallized ligands. The binding affinity against snake acetylcholinesterase was -8 greater than -5 of the co-crystallized-ligand. Cobra cardiotoxin had docking score of -5.4 and -5.1 against

Table2: Selected Snake Venom Protein Targets

NO.	Target Protein ID
1.	1FSS Snake acetylcholinesterase
2.	4OM4 Snake venom cardiotoxin
3.	4Z5R Interferon 2A
4.	5M2J Tumor necrosis factor alpha
5.	1BUD Snake Hemorrhagic metalloproteinase (acutolysin)
6.	5GZ5 Snake Phosphodiesterase

chloroquine and co-crystallized ligand respectively. While the binding energies for Interferon 2a, tumor necrotic factor, snake venom acutolysin and Snake venom phosphodiesterase were -5.6 & -4.2, -6.2 & -3.1, -5.3 & -1.3 and -6.2 & -6.2 for chloroquine and co-crystallized ligands respectively. See table 3 and appendix 1.

Table 3: Docking Results of the Snake Venom Proteins Against Chloroquine and the Co Crystallized Ligands

Protein target	Binding Score	
	Chloroquine	Co crystallized ligand
1fss (Snake acetylcholinesterase)	-8	-5.2
4om4 (Cobra cardiotoxin)	-5.4	-5.1
4z5r (Interferon 2a)	-5.6	-4.2
5m2j (Tumor Necrotic factor)	-6.2	-3.1
1bud (Snake venom acutolysin)	-5.3	-1.3
5gz4 (Snake venom phosphodiesterase)	-6.2	-6.2

Two-dimensional Structure of Chloroquine and 3D Structures of the Snake Venom Proteins

The 2-dimensional structure of chloroquine, a 4-aminoquinoline was downloaded from drugbank. (Figure 1). While the 3-dimensional structure of the six snake venom proteins with multiple amino acids chains were also downloaded from the protein data bank. See Figure 2.

Figure 1. 2D Structure of Chloroquine

Figure 2. 3D Structure of the Snake venom proteins

Chloroquine Superimposing to the Active Pocket of the six snake venom proteins

Chloroquine superimposes with the active pocket of the snake venom proteins (Figure 3).

Figure 3: 3D Interaction of Chloroquine and the Snake venom protein

Comparative analysis of the 2D Interactions for Chloroquine with snake Venom Proteins

Chloroquine interact with amino acids residues (GLU 69, MET 61, ARG 38, LEU 73 and MET 65) at the active site of snake phosphodiesterase. Again, Chloroquine interact with amino acids residues (MET 61, MET 62, MET 65, ALA 58, LEU 73 and GLU 69) at the active site of snake cardiotoxin. Similarly, Chloroquine interact with amino acids residues (GLY 174, PHE 178, PHE 126, PHE 106, TYR 155, TYR 105, ASN 161, MET 154, GLU 150 and PHE 131) at the active site of snake acutolysin. Correspondingly, Chloroquine interact with amino acids residues (ILE 119, ILE 54, GLU 122, VAL 26 and ALA 98) at the active site of snake acetylcholinesterase. See Figure 4.

Ligand-Based Pharmacophore of Chloroquine

The generated pharmacophore for chloroquine (hydrogen bond acceptor, positive ionizable areas and hydrophobic interactions) were located on the benzene ring and the and the 4-amino side chain. See Figure 5.

Discussion

Chloroquine is a 4-aminoquinoline with antimalarial, anti-inflammatory, and potential chemo-sensitization and radio-sensitization activities^{14,15}. Chloroquine has been recognized as a miracle or magic medicine to treat malaria, autoimmune diseases, cancer, viral, dermatological, and fungal infections.^{16,17} Considering the diversity of its pharmacological actions, it is likely that other potential mechanisms may exist in its action against other targets. In this study, chloroquine was assessed for its direct effects, by docking it against the snake venom target proteins.

The hierarchical approach (funnel principle) in computational drug discovery in which different methods are combined consecutively is a reliable, validated and high precision method, where at each consecutive step the compounds most unlikely to be active are removed, leaving

Figure 4: 2D Interaction of Chloroquine and the Snake Venom Proteins

Typically, every step of the hierarchical approach consists of a more complex, computationally demanding step than the previous one. As such, pharmacophore models are utilized as a filter to identify compounds that fulfill simple geometric and chemical functionality requirements of the query, prior to a more complicated and computationally demanding molecular docking approach.¹⁸

PI- Positive ionizable areas, HBA- Hydrogen bond donor, H- Hydrophobic interactions
Figure 5. Pharmacophore of Chloroquine

The aim of this study was to identify another indication for chloroquine using PASS ONLINE target identification, molecular docking and pharmacophore modelling approach. Six (6) snake venom proteins were selected from the PASS online screening software as potential targets for chloroquine. These targets include; snake acetylcholinesterase, snake venom cardiotoxin, interferon 2A, tumor necrosis factor alpha, snake hemorrhagic metalloproteinase (acutolysin), and snake phosphodiesterases. The snake autolysin exhibits several biological effects including local and systemic hemorrhagic activities myonecrosis, and disruption of hemostasis and platelet aggregation.¹⁹ While, snake phosphodiesterases enhances the inactivation of cAMP, a second messenger

necessary for homeostasis and regulation of metabolic processes.²⁰ The poisonous snake acetylcholinesterase terminates cholinergic and neuromuscular junction synaptic transmission by hydrolyzing acetylcholine into choline and acetic acid.²¹ Snake venom cardiotoxin is a non-enzymatic neuro- and cardio toxin that act by binding to postsynaptic neuro-muscular and neuro-effector sites producing flaccid paralysis and ischemic heart diseases.²² Finally, the Interferon 2A and tumor necrosis factor alpha induces the inflammatory and immune-modulatory changes and responses leading to systemic envenomation.²³ Chloroquine demonstrated excellent binding affinities (when compared to the co-crystallized ligands) against the six snake venom proteins. Additionally, it fits into the active pockets of the six targets. Again, chloroquine interacts with the amino acid residues of the protein targets at its pharmacophore sites (HBA, PI, NI, and hydrophobic areas). These findings showed the ability chloroquine to effectively bind to these targets thereby inhibiting their effects. Though several studies have attempted to repurpose chloroquine for other indications.^{3,24-29} This study was the first to predict the activity of chloroquine against snake venom targets. This approach is more practical and less expensive than discovery of novel compounds that will require toxicity studies

Conclusion

Chloroquine might be a cheaper, less toxic, readily available and effective alternative to anti-snake venom in the management of snake bite.

Recommendation

Future confirmation of this activity using validated in vivo model is recommended.

Acknowledgement

We are grateful to Prof. S.O Bello for the wonderful mentorship.

Conflict of Interest

None

References

- Cooper R, Magwere T. Chloroquine: novel uses & manifestations. *Indian Journal of Medical Research*. 2008;127(4).
- Warrell DA. Clinical toxicology of snakebite in Africa and the Middle East/Arabian Peninsula. *Handbook of: Clinical Toxicology of Animal Venoms and Poisons*: CRC Press; 2017. p. 433-92.
- Zhou W, Wang H, Yang Y, Chen Z-S, Zou C, Zhang J. Chloroquine against malaria, cancers and viral diseases. *Drug Discovery Today*. 2020.
- Goel P, Gerriets V. Chloroquine. 2019.
- Chippaux J-P. Snakebite envenomation turns again into a neglected tropical disease! *Journal of Venomous Animals and Toxins including Tropical Diseases*. 2017;23.
- Gómez-Betancur I, Gogineni V, Salazar-Ospina A, León F. Perspective on the therapeutics of anti-snake venom. *Molecules*. 2019;24(18):3276.
- Rahmani AH, Jalali A, Alemzadeh-Ansari MH, Tafazoli M, Rahim F. Dosage comparison of snake anti-venom coagulopathy. *Iranian journal of pharmaceutical research: IJPR*. 2014;13(1):283.
- Weinstein SA. Non-front-fanged colubroid snakes. *Critical Care Toxicology* Springer Verlag. 2017:2453-92.
- Murtazaliev K, Druzhilovskiy D, Goel R, Sastry G, Poroikov V. How good are publicly available web services that predict bioactivity profiles for drug repurposing? SAR and QSAR in Environmental Research. 2017;28(10):843-62.
- Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The protein data bank. *Nucleic acids research*. 2000;28(1):235-42.
- Wishart DS. DrugBank and its relevance to pharmacogenomics. 2008.
- Ellingson SR, Baudry J. High-throughput virtual molecular docking with AutoDockCloud. *Concurrency and Computation: Practice and Experience*. 2014;26(4):907-16.
- Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Chemical biology*: Springer; 2015. p. 243-50.
- Martinez GP, Zabaleta ME, Di Giulio C, Charris JE, Mijares MR. The role of chloroquine and hydroxychloroquine in immune regulation and diseases. *Current Pharmaceutical Design*. 2020;26(35):4467-85.
- Ferreira PMP, Ferreira JRdO, Sousa RWRd, Bezerra DP, Militão GCG. Aminoquinolines as Translational Models for Drug Repurposing: Anticancer Adjuvant Properties and Toxicokinetic-Related Features. *Journal of Oncology*. 2021;2021.
- Kamat S, Kumari M. Repurposing chloroquine against multiple diseases with special attention to SARS-CoV-2 and associated toxicity. *Frontiers in Pharmacology*. 2021;12.
- Chang R, Sun W-Z. Repositioning chloroquine as antiviral prophylaxis against COVID-19: potential and challenges. *Drug discovery today*. 2020;25(10):1786-92.
- Qing X, Lee XY, De Raeymaecker J, Tame JR, Zhang KY, De Maeyer M, et al. Pharmacophore modeling: advances, limitations, and current utility in drug discovery. *Journal of Receptor, Ligand and Channel Research*. 2014;7:81-92.
- Gâz Florea ȘA, Gâz Florea A, Kelemen H, Muntean D-L. Snake Venom Metalloproteinases. *Acta Medica Marisensis*. 2016;62(1).
- Marcelo KL, Means AR, York B. The Ca²⁺/calmodulin/CaMKK2 axis: Nature's metabolic CaMshaft. *Trends in Endocrinology & Metabolism*. 2016;27(10):706-18.
- Tripathi A, Srivastava U. Acetylcholinesterase: a versatile enzyme of nervous system. *Annals of Neurosciences*. 2010;15(4):106-11.
- Wong KY, Tan KY, Tan NH, Tan CH. A Neurotoxic Snake Venom without Phospholipase A2: Proteomics and Cross-Neutralization of the Venom from Senegalese Cobra, *Naja senegalensis* (Subgenus: *Uraeus*). *Toxins*. 2021;13(1):60.
- Lu L. Self-assembling Peptide Based Nanoscaffolds to Manipulate the Inflammatory Responses. 2017.
- Parvathaneni V, Gupta V. Utilizing drug repurposing against COVID-19-Efficacy, limitations, and challenges. *Life sciences*. 2020;118275.
- Pallaval VB, Kanithi M, Meenakshisundaram S, Jagadeesh A, Alavala M, Pillaiyar T, et al. Chloroquine Analogs: An Overview of Natural and Synthetic Quinolines as Broad Spectrum Antiviral Agents. *Current Pharmaceutical Design*. 2021;27(9):1185-93.
- Fong W, To KK. Repurposing Chloroquine Analogs as an Adjuvant Cancer Therapy. *Recent Patents on Anti-Cancer Drug Discovery*. 2021;16(2):204-21.
- Naghipour S, Ghodousi M, Rahsepar S, Elyasi S. Repurposing of well-known medications as antivirals: hydroxychloroquine and chloroquine—from HIV-1 infection to COVID-19. *Expert Review of Anti-infective Therapy*. 2020;18(11):1119-33.
- Wong SK. Repurposing New Use for Old Drug Chloroquine against Metabolic Syndrome: A Review on Animal and Human Evidence. *International journal of medical sciences*. 2021;18(12):2673.
- Srivastava V, Lee H. Chloroquine-based hybrid molecules as promising novel chemotherapeutic agents. *European journal of pharmacology*. 2015;762:472-86.