IOSR Journal of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 15, Issue 12 Series. I (December 2025), PP.25-34
www.iosrphr.org

A Recent Review on Novel Derivatives of Hydroxychloroquine

Aditi[1], *Dr.Abhishek Soni[2], Ms.Pooja Devi[2]
[1]Research Scholar, [2] Assistant Professor, [3]Assistant Professor
School of Pharmacy, Abhilashi University, Chailchowk, Himachal Pradesh, India

Abstract:
Malaria is an acute febrile disease that is caused due to the parasite infection, transmitted in humans by female anopheles mosquito bite. Malaria is one of the leading reasons of mortality worldwide, but the early detection and quick acting treatment can fend off these unpleasant results. In Africa and some Asian countries, malaria is the most common disease,while in other developed countries it occurs due to import from endemic countries. As early as the 2nd century BC Chinese people used sweet sagewort plant to cure malarial fever. Quinine began to be used as an anti-malarial drug much later. A worldwide fight in oppose to malaria began in 1955. Croatia became malaria free in 1964 and declared this year as malaria eradication year. The WHO (world health organization) runs malaria control programs on global level with a focus on primary health care, early detection, quick treatment and preventions. Now these days the load of malaria is lowered down than it was 10 years ago. Although the number of patients suffering from malaria have been increased in the world. The progress has fallen off but the targets of world health organization are moving forward.
Keywords: Malaria, Hydroxychloroquine, Nano-technological strategies and Nanoject.

I. INTRODUCTION:

About 219 million people were suffering from malaria globally in 2017 and it caused deaths of 435,000 people. This mortality and morbidity burden is the fruit of worldwide research on malarial prevention and treatment after more than a century.In Africa malaria is a common disease and in some Asian countries there is biggest number of cases. Globally the mortality rate due to malaria is 0.3-2.2% and in tropical areas it is 11-30%. Various studies have shown that since 2015 malarial parasite infection has increased. Malaria is caused by a single celled protozoan of plasmodium specie group. [1] It has various more subspecies. Some of these subspecies can cause disease conditions in humans. Plasmodium falciparum is the most common specie in African countries but in American and European countries Plasmodium vivax and plasmodium malarial are more common. [2] There is an anti-malarial medication known as Hydroxychloroquine which is being sold under the trading name of Plaquenil. This drug is used in disease like rheumatoid arthritis and lupus to reduce inflammation. [3] The presence of hydroxyl group at the end of side chain makes Hydroxychloroquine different from chloroquine; the N-ethyl substituent is beta-hydroxylated. It is administered orally in the form of Hydroxychloroquine sulphate. It is an important medication in the list of WHO, which is the basic health system's most essential drugs list. [4]

1. Life Cycle, Diagnosis and Treatments And Combination Therapy Used For Malaria:

In 2013 about 198 million cases were found causing 584,000 deaths as per latest estimation. 47% of malarial mortality rates have lowered down globally since 2000 to 2013. Most of deaths happened in Africa are child mortality, a child dies of malaria every minute. Since 2009, 58% malaria mortality rates have been fallen in Africa. [5]

1.1 Lifecycle of the Malaria:

Through a vector malarial transmission happens, when a mosquito is feeding on an individual who is infected, it swallows the gametocytes. These gametocytes are injected to the other human while mosquito having next feed of blood. In that next individual they infect hepatocytes and start asexual replication. The schizonts begin to rupture after 6-15 days and merozoites are released in to blood in thousands in numbers. [6] Then they attack red blood cells in which these parasites develop in a set and nearly 16 new daughter cells of merozoites produce from each schizont. One or more of four intracellular protozoan parasite species i.e Plasmodium Falciparum, Plasmodium Ovals, Plasmodium Vivax, and Plasmodium Malariae are the causes of Malarial infection in humans.[7]

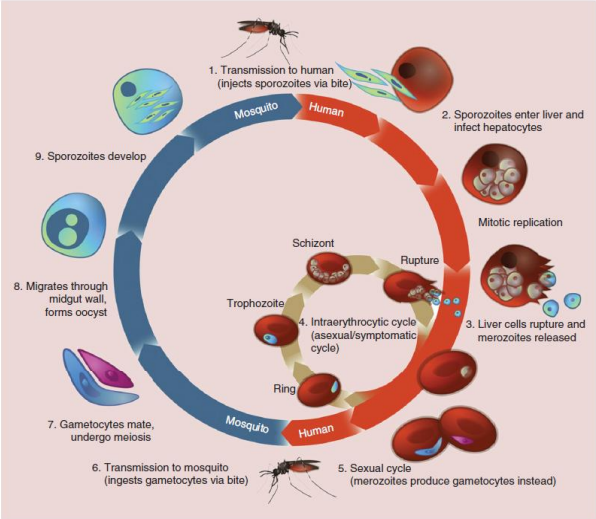

Figure: - Stages of Life Cycle of Malaria.

Life Cycle of Malaria (Stages) and Drugs for Life Cycle of Malaria (Stages):

Stage I: In first stage by the mosquito bite plasmodium sporozoites get in to individual's body and there is no effect of any drug in the first stage.

Stage II: Sporozoites get into hepatocytes merozoites stage creates pyrimethamine and Primaquine are the drugs that can block in this stage.

Stage III: In third stage hepatocytes release merozoites to enter in RBCs and produce more merozoites that causes bursting of RBCs. In this stage individual suffers from pyrexia, hence only Primaquine can help in this stage.

Stage IV: More RBCs continue to get infected by merozoites which cause fever and chills in the individual. Drugs that can block in this stage are like chloroquine, amodiaquine, santoquine, proguanil.

Stage V: Gametocytes are produced by some merozoites that are sexual structures which can be taken away by mosquito to infect others. Only Primaquine is helpful in this condition. [8] and [9].

1.2 DIAGNOSIS:

On stained blood films intracellular examination direct microscopic examination is standard conclusive way of diagnosis these days in almost all settings. Although there are many other methods in existence or some other are under development which will be described. [10]

Clinical Diagnosis:

- **Antigen detection tests (Rapid or Dipstick Test):**

The third diagnostic approach necessitates the immunochromatographic methods to employ the rapid detection of parasite antigen. Several tests are created that target different parasite antigen. This method has the advantages that there is no need of any specific equipment, small training is needed, the temperature is constant for the test and reagents and there is no need to use electricity. The disadvantages of this method are that it is expensive and this method is unable to tell infection density. Moreover, antigens that are detectable preserve for few times even after sufficient treatment and heal. [11]

- **Molecular tests:**

PCR is most useful tool for detecting the parasite genetic material and also diagnose anti-malarial drug resistance surveillance. Especially for every human malarial species, primers are developed. An important use of the method is that it can detect mixed infection of different species and can also differentiate between them during examination under microscope. [12]

- **Serology:**

This method detects antibodies against malarial parasites in samples of serum. For each malarial species that can affect humans different specific identification serological markers are identified. A past infection is identified by positive test. To Diagnose the acute infection this test is not useful for the reason that the levels in which the malarial antibodies against parasites are detectable appear after weeks and continue so long. And also this test is comparatively costly and not available that much. [13]

1.3 Available Drugs to treat Malaria:

The drugs that are used for treatment and prevention of malaria are available in limited numbers only. Quinine and its other derivatives and anti-folate for combination are most commonly used drug for malaria.[14]

- **Quinine and related compounds:**

Quinine, with its dextroisomer quinidine has become a drug that is last option to treat malaria especially in severe cases. A 4-aminoquiolineis the quinine related component i.echloroquine was synthesized in 1934 and is most commonly used anti-malarial drug. Moreover, Primaquine and mefloquine are other derivative of quinine that are used commonly.. [14] and [15]

- **Anti-folate combination drugs:**

These medications are several combinations of sulfa drugs with dihydrofolate reductase inhibitors. Despite the fact that these medications, when used alone have antimalarial action and resistance against parasites can create in rapid process. The symbiotic effect on parasites is created when they are used in combination and even in the existence of individual component resistance they are effective. [14] and [16]

- **Antibiotics**

There are some antibiotics such as tetracycline and its related compounds like doxycycline are very effective against malaria. Tetracycline and quinine are used often in combination to cure malaria, when the quinine effect is out of gear. Clindamycin is also being used but it gives only few advantages as compare to other antimalarial drugs which are easily available. [14] and [17]

- **Artemisinin compounds:**

From the plant Artemisia annua i.e. sweet wormwood several sesquiterpenes lactone compounds are obtained e.g. artesunate, arteether and arteether.[14] and [18]

- **Miscellaneous compounds:**

A phenanthrenemethanol compound, halofantrine keeps the activities to fight against the malarial parasites at erythrocytic stage. [19] Atovaquone that is a Hydroxynaphthoquine is presently being most commonly used as the opportunistic infection treatment in the patients who are immunosuppressed. [20] In China, two drugs are synthesized that are Pyronaridine and Lamefantrinel. Pyronaridine is reported 100% effectual in Cameroon in first trial;but it was only 63-88% fruitful in Thailand. The other drug Lamefantrinel, a compound of fluromenthanol, is used as combination medication with artemether in it. [21]

1.4 Antimalarial Combination Therapy:

When the two anti-malarial drugs are used together, they have power to hold back the increase in resistance of any component, especially when both drugs have different modes of action. [22] The ability of the combination of 4-aminoquinoline drug i.echloroquine/amodiaquine and sulfadoxine/ pyrimethamine was analysed. and they got the results that if chloroquine or amodiaquine is added to sulfadoxine/pyrimethamine the clearance of parasites as compare to alone SP The approach of other drug combination, derivative of artemisinin with other antimalarial drugs. [23] and [24].

2. Hydroxychloroquine:

An anti-malarial medication known as Hydroxychloroquine which is being sold under the trading name of Plaquenil. [25] This drug is used in disease like rheumatoid arthritis and lupus to reduce inflammation. The presence of hydroxyl group at the end of side chain makes Hydroxychloroquine different from chloroquine; the N-ethyl substituent is beta-hydroxylated. [26] It is administered orally in the form of Hydroxychloroquine sulphate. It is an important medication in the list of WHO which isthe basic health system's most essential drugs list. [27] and [28]

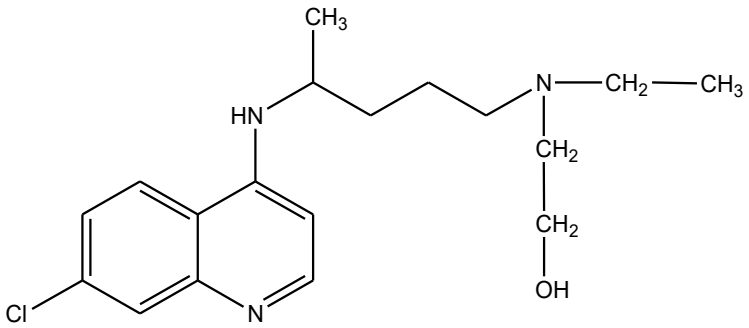

Figure :- Structure of Hydroxychloroquine

2.1 Chemical Profile, Pharmacokinetics and Pharmacodynamics:

Chemical Profile:

The Hydroxychloroquine is a White Crystalline Solid. The Systematic (IUPAC) name of Hydroxychloroquine is 2-[[4-[(7-Chloro-4-quinolyl) amino] pentyl] ethyl amino] ethanol. $C_{18}H_{26}ClN_3O$ is the molecular formula and 335.9 g/mol molar masses. [29]

Pharmacokinetics:

The Tmax is 2-4.5 hours and on average bioavailability was 74% and protein binding is around 45%. Metabolism occurs in the Liver. The Biological half-life is 32–50 days and Excretion occurs through the Kidney (23–25%). Hydroxychloroquine and chloroquine have comparable pharmacokinetics with rapid GIT absorption. N-desethylhydroxychloroquine is produced as a result of its metabolism by the cytochrome-P450 enzymes CYP2D6, 2C8, 3A4, and 3A5. [31] and [32]

Pharmacodynamics:

Anti-malarial drugs are weak bases that are lipophilic and readily cross plasma membranes. Reduced proteolysis results from lysosomal acidic proteases being inhibited by pH changes. [33] These effects are thought to be the reason for diminished immune cell activity, including neutrophil chemotaxis, phagocytosis, and superoxide generation. Anti-malarial drugs are weak bases that are lipophilic and readily cross plasma membranes. Reduced proteolysis results from lysosomal acidic proteases being inhibited by pH changes. [34] These effects are thought to be the reason for diminished immune cell activity, including neutrophil chemotaxis, phagocytosis, and superoxide generation. [34] and [35]

2.2 Rationale of Polymer Drug Conjugates:

It may be of interest to synthesize and test the polymer-linked Hydroxychloroquine Prodrugs when liver toxicity is taken into account. These Prodrugs are anticipated to transport Hydrochloroqunine to the liver specifically, killing localized parasites while also preventing medication resistance. [36]

- **Polyphosphazene:**

The ability to attach a wide range of substituents to the phosphorus atom leads in a very broad spectrum of physicochemical features for biomedical applications and polymeric drug delivery systems, making polyphosphazenes the most adaptable inorganic polymers. [37]

- **Bioactive Polyphosphazenes:**

It is generally accepted that chemotherapeutic medications' efficiency can be increased by directing them to particular locations inside the body and by allowing for a controlled release of the drug to maintain optimal concentration. [38] It has been discovered that several Polyphosphazenes degrade hydrolytically in aqueous media. These are polymers that feature amino acid ester or imidazole side groups, and researchers have also created water-soluble polymers with glucose side groups. [39]

- **Organometallic Polyphosphazenes:**

The use of polymer-bound transition metal systems as electro-active materials and catalyst systems is of interest. Provided that each skeletal phosphorus atom has an electron-supplying side group attached, the backbone nitrogen atoms of Polyphosphazenes are very basic. [40] Organometallic units like CO2 $(CO)_6$ can bond to Phosphazenes-skeleton-attached pendent acetylenic units. To create polymer-bound catalytic systems, pendent nido-carboranyl groups bond to transition metal units like Rh(PPh3)2H groups. [41]

Nano-technological strategies for drug targeting in malaria therapy:

The purpose of employing nano-carriers as drug delivery methods is to improve selectivity, decrease frequency of administration and length of therapy, and enhance the pharmacokinetic profile of the drug by promoting drug or vaccine protection against extracellular degradation.[42]

Hydroxychloroquine-conjugated gold nanoparticles:

More powerful dosages of siRNA are currently delivered to tumours using pharmaceutical dosage forms. The siRNA-conjugated PEGylated gold nanoparticles' intracellular and silencing activity is affected by Hydroxychloroquine conjugation, which can improve gene down regulation. [43]

Nanostructured lipid carriers of Artemether–Lamefantrinel:

Due to their reduced cognition and vomiting, patients with cerebral malaria are unable to take oral medications, necessitating parenteral therapy. There are downsides to each of the current parenteral malaria treatments used: quinine, ARM, and artesunate. In order to cure malaria, the WHO currently forbids mono-therapy and suggests artemisinin-based combination therapy. A WHO-approved combination for oral malaria medication is ARM-LFN.[44] and [45].

- **Chitosan nanoparticles of curcumin:**

Curcumin bound to chitosan nanoparticles to increase its bioavailability and chemical stability. It can be observed that curcumin bound to chitosan nanoparticles did not degrade much faster in comparison to free curcumin.[46]

- **Double stranded RNA nanoparticles:**

A possible avenue for the development of anti-malarial medicine is based on RNA intervention targeting expression of DNA topoisomerase II, a critical gene for the malaria parasite. DNA and tiny double-stranded invasive RNA can be delivered to target cells using biodegradable chitosan nanoparticle systems. To prevent cognate mRNA expression and test its effects on P. falciparum development in culture, a long double-stranded (dsRNA) targeting the coding region to complexes with chitosan nanoparticles has been created.[47] and [48]

- **Hydrogel nanoparticles of curcumin:**

For the creation of hydrogel nanoparticles, polyvinyl pyrrolidone and hydroxyl propyl methyl cellulose can be combined. Due to a potential evasion of the reticular-endothelial system, the goal is to construct nano carriers to boost absorption and extend the quick clearance of curcumin.[49]

- **Antisense nanoparticles:**

Malaria topoisomerase-II gene silencing by ODNs was revealed to acquire promising properties as an anti-malarial drug. In order to improve stability and promote intracellular penetration, ODNs combines with the biodegradable polymer chitosan to produce solid nanoparticles with an initial diameter of 55 nm. [50]

- **Albumin-bound nanoparticles:**

The indolone-N-oxides have been investigated as potential treatments for malaria that is resistant to chloroquine. The extremely poor aqueous solubility of these compounds, which results in weak and unpredictable action, has, however, hindered in vivo testing. Precipitation and high-pressure homogenization can be used to create nanoparticles. [53] The procedure may be improved to produce nanoparticles with a restricted size distribution and controllable diameter that are suited for intravenous delivery and that clearly demonstrated direct drug contact with parasitized erythrocytes. In comparison to 1.5% of pure medication, stable nanoparticles had a significantly higher rate of solubility and maintained the rapid antimalarial activity. Comparable to artesunate and chloroquine, the formulation completely cured Plasmodium berghei-infected mice at a dose of 25 mg/kg by reducing parasitaemia (99.1%) and extending survival time and preventing recrudescence.[52]

- **Nano structured lipid carrier (NLC) of glyceryl-dilaurate (GDL):**

GDL-NLCs have a direct effect on plasmodium parasite-infected RBCs, which results in severe impairment. The targeting can be accomplished by using the glyceryl-dilaurate lipid moiety. GDL-NLCs were found on the parasite mitochondrion, and their uptake resulted in the polarisation of the mitochondrial membrane, the accumulation of Ca2+ ions, stage-specific RBC lyses, and the release of ROS.[53] and [54].

- **Gold nanoparticles of marine Actinobacterial and antimalarial:**

Gold nanoparticles (Au-N-LK3) mediated by Streptomyces sp. LK-3 can be synthesised in the size range of 5–50 nm. Plasmodium berghei ANKA (PbA)-infected mice were treated with Au-N-LK3, which was reported to be effective in delaying parasitaemia rises compared to PbA infection at 8 days after infection. [55]

- **Nano-emulsion and Porous Polymeric Nanoparticles:**

The antigen CHrPfs25, which prevents the spread of malaria, can be made using nano-emulsions (NE) and poly (D, L-lactide-co-glycolide) nanoparticles (PLGA-NP) and tested in mice via intramuscular injection. The conventional mosquito membrane feeding test, which evaluates the effectiveness of antibodies at preventing transmission, can be used with pure IgG from immune sera.[56] and [57]

- **Green synthesized silver nanoparticles**

In the recent study silver nanoparticles have been synthesized from $AgNO_3$ (Silver Nitrate) through simple green routes using either purified Alpha Amylase or aqueous leaf extracts of Asoka and Neem respectively. The use of plant extract for synthesis of NPs is an ecological process and cost efficient. The synthesized NPs can be established to be anti-plasmodium with IC_{50} (µg/ml) 3.75 (Amylasenp), 8 (Ashokanp) and (Neemnp) while plant extracts or amylase alone do not show any activity up to 40 µg/ml. [59]

- **Gold nanoparticles of *Couroupitaguianensis:***

Using a cheap floral extract of Couroupita guianensis as a stabilising agent, AuNPs can be produced organically. The bio production of AuNP, particle size, and zeta potential can be verified using techniques like Fourier transform infrared (FTIR) spectroscopy, transmission electron microscopy (TEM), UV-vis spectrophotometer, energy-dispersive X-ray (EDX) spectroscopy, etc. Both the CQ-sensitive (CQ-s) and CQ-resistant (CQ-r) strains of Plasmodium falciparum can be tested for antiplasmodial activity simultaneously using the flower extract of Couroupita guianensis and AuNS.[60] and [61]

- **Polyphosphazene based nanoparticles of Primaquine and Dihydroartemisinin:**

Primaquine and dihydroartemisinin nanoparticles based on Polyphosphazene have been developed and tested in a mouse model of P. berghei infection. Compared to the usual drug combination, the combination showed promise antimalarial activity at lower doses. [62] Further evidence that this combination medication is effective

against resistant malaria comes from the fact that it offered protection for 35 days without any recurrence. The study offers a different combination regimen that has been discovered to be successful in the treatment of resistant malaria. [63]

- **Nanostructured lipid carrier of artemether:Nanoject:**

Artemether is a very ineffective antimalarial drug. In the most recent study, the possibility of a nanostructured lipid carrier was investigated for the i.v. delivery of artemether. The artemether nano structured lipid carrier can be created using the micro emulsion template process. Mice with Plasmodium berghei infection can be used to test the antimalarial efficacy of an intravenous formulation. ARM was continuously released from the nanoject.[64]

- **Monensin Loaded PLGA Nanoparticles:**

PLGA with molecular weights between 19 000 and 110 000 Da can be used to create PLGA nanoparticles that are loaded with carboxylic ionophore utilising the emulsion solvent evaporation method. One can test the antimalarial effectiveness of monensin-PLGA nanoparticles. Monensin loaded in nanoparticles can be up to 10 times more effective at preventing P. falciparum growth than free monensin.[65]

- **Silver nanoparticles using leaves of *Catharanthus roseus* Linn. G. Don:**

Utilizing Catharanthus roseus Linn's aqueous leaf extracts, new silver nanoparticles can be created. A document that displays activity against the malaria pathogen Plasmodium falciparum has been generated (P. falciparum). Energy dispersive X-ray, X-ray diffraction, ultraviolet-visible (UV-Vis) spectrophotometry, and SEM can all be used to characterise the produced silver nanoparticles.[66]

- **Transferrin-conjugated solid lipid nanoparticles:**

For the treatment of cerebral malaria, the Transferrin (Tf)-conjugated SLNs can be studied for the delivery of quinine dihydrochloride to the brain. Fluorescence tests showed that Tf-SLNs were more readily absorbed in brain tissue than unconjugated SLNs. [64]

II. CONCLUSION:

Quinine, with its dextroisomer quinidine has become a drug that is last option to treat malaria especially in severe cases. A possible avenue for the development of anti-malarial medicine is based on RNA intervention targeting expression of DNA topoisomerase II. DNA and tiny double-stranded invasive RNA can be delivered to target cells using biodegradable chitosan nanoparticle systems.Nanostructured lipid carrier of artemether can be used for the i.v. delivery of anti-malaria drugs. Monensin loaded in nanoparticles can be up to 10 times more effective at preventing P. falciparum growth than free monensin.

REFERENCES:

[1]. Garcia LS. Malaria. Clin Lab Med. 2010 Mar;30(1):93-129. doi: 10.1016/j.cll.2009.10.001. PMID: 20513543.

[2]. Lover AA, Baird JK, Gosling R, Price RN. Malaria Elimination: Time to Target All Species. Am J Trop Med Hyg. 2018 Jul;99(1):17-23. doi: 10.4269/ajtmh.17-0869. Epub 2018 May 10. PMID: 29761762; PMCID: PMC6035869.

[3]. Ishtiaq F, Swain S, Kumar SS. Anopheles stephensi (Asian Malaria Mosquito). Trends Parasitol. 2021 Jun;37(6):571-572. doi: 10.1016/j.pt.2021.03.009. Epub 2021 Apr 14. PMID: 33865712.

[4]. Bilgin ZD, Evcil I, Yazgi D, Binay G, OkuyucuGenc C, Gulsen B, Huseynova A, Ozdemir AZ, Ozmen E, Usta Y, Ustun S, CaglarAndac S. Liquid Chromatographic Methods for COVID-19 Drugs, Hydroxychloroquine and Chloroquine. J Chromatogr Sci. 2021 Aug 18;59(8):748-757. doi: 10.1093/chromsci/bmaa110. PMID: 33336246; PMCID: PMC7799265.

[5]. Talapko J, Škrlec I, Alebić T, Jukić M, Včev A. Malaria: The Past and the Present. Microorganisms. 2019 Jun 21;7(6):179. doi: 10.3390/microorganisms7060179. PMID: 31234443; PMCID: PMC6617065.

[6]. Soulard V., Bosson-Vanga H., Lorthiois A., Roucher C., Franetich J.-F., Zanghi G., Bordessoulles M., Tefit M., Thellier M., Morosan S., et al. Plasmodium falciparum full life cycle and Plasmodium ovale liver stages in humanized mice. *Nat. Commun.* 2015;6:7690. doi: 10.1038/ncomms8690.

[7]. Ranadive N., Kunene S., Darteh S., Ntshalintshali N., Nhlabathi N., Dlamini N., Chitundu S., Saini M., Murphy M., Soble A. Limitations of Rapid Diagnostic Testing in Patients with Suspected Malaria, A Diagnostic Accuracy Evaluation from Swaziland, a Low-Endemicity Country Aiming for Malaria Elimination. *Clin. Infect. Dis.* 2017;64:1221. doi: 10.1093/cid/cix131.

[8]. Kozycki C.T., Umulisa N., Rulisa S., Mwikarago E.I., Musabyimana J.P., Habimana J.P., Karema C., Krogstad D.J. False-negative malaria rapid diagnostic tests in Rwanda: Impact of Plasmodium falciparum isolates lacking hrp2 and declining malaria transmission. *Malar. J.* 2017;16:123. doi: 10.1186/s12936-017-1768-1.

[9]. Rougemont M., Van Saanen M., Sahli R., Hinrikson H.P., Bille J., Jaton K. Detection of Four Plasmodium Species in Blood from Humans by 18S rRNA Gene Subunit-Based and Species-Specific

Real-Time PCR Assays. *J. Clin. Microbiol.* 2004;42:5636–5643. doi: 10.1128/JCM.42.12.5636-5643.2004.

[10]. Draper S.J., Sack B.K., King C.R., Nielsen C.M., Rayner J.C., Higgins M.K., Long C.A., Seder R.A. Malaria Vaccines, Recent Advances and New Horizons. *Cell Host Microbe.* 2018;24:43–56. doi: 10.1016/j.chom.2018.06.008.

[11]. Connolly P, Hage CA, Bariola JR, Bensadoun E, Rodgers M, Bradsher RW Jr, Wheat LJ. Blastomyces dermatitidis antigen detection by quantitative enzyme immunoassay. Clin Vaccine Immunol. 2012 Jan;19(1):53-6. doi: 10.1128/CVI.05248-11. Epub 2011 Nov 23. PMID: 22116687; PMCID: PMC3255946.

[12]. Zheng Z, Cheng Z. Advances in Molecular Diagnosis of Malaria. Adv Clin Chem. 2017;80:155-192. doi: 10.1016/bs.acc.2016.11.006. Epub 2017 Feb 22. PMID: 28431639.

[13]. Kyomuhangi I, Giorgi E. A unified and flexible modelling framework for the analysis of malaria serology data. Epidemiol Infect. 2021 Apr 12;149:e99. doi: 10.1017/S0950268821000753. PMID: 33843523; PMCID: PMC8161365.

[14]. White NJ. The treatment of malaria. N Engl J Med. 1996 Sep 12;335(11):800-6. doi: 10.1056/NEJM199609123351107. PMID: 8703186.

[15]. Lefrère B, Barbaud A, Bagot M, Bourgogne E. Eau tonique et quinine – un cocktail de bicentenaireservi en pleine effervescence [Tonic water and quinine-a bicentennial booming cocktail]. Rev FrAllergol (2009). 2021 Oct;61(6):425-431. French. doi: 10.1016/j.reval.2021.04.002. Epub 2021 May 12. PMID: 33995692; PMCID: PMC8114147.

[16]. Ding S, Ye R, Zhang D, Sun X, Zhou H, McCutchan TF, Pan W. Anti-folate combination therapies and their effect on the development of drug resistance in Plasmodium vivax. Sci Rep. 2013;3:1008. doi: 10.1038/srep01008. Epub 2013 Jan 7. PMID: 23301149; PMCID: PMC3538286.

[17]. Gaillard T, Madamet M, Tsombeng FF, Dormoi J, Pradines B. Antibiotics in malaria therapy: which antibiotics except tetracyclines and macrolides may be used against malaria? Malar J. 2016 Nov 15;15(1):556. doi: 10.1186/s12936-016-1613-y. PMID: 27846898; PMCID: PMC5109779.

[18]. Chen GQ, Benthani FA, Wu J, Liang D, Bian ZX, Jiang X. Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis. Cell Death Differ. 2020 Jan;27(1):242-254. doi: 10.1038/s41418-019-0352-3. Epub 2019 May 21. PMID: 31114026; PMCID: PMC7205875.

[19]. Yarom N, Hovan A, Bossi P, Ariyawardana A, Jensen SB, Gobbo M, Saca-Hazboun H, Kandwal A, Majorana A, Ottaviani G, Pentenero M, Nasr NM, Rouleau T, Lucas AS, Treister NS, Zur E, Ranna V, Vaddi A, Barasch A, Lalla RV, Cheng KKF, Elad S; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO). Systematic review of natural and miscellaneous agents, for the management of oral mucositis in cancer patients and clinical practice guidelines - part 2: honey, herbal compounds, saliva stimulants, probiotics, and miscellaneous agents. Support Care Cancer. 2020 May;28(5):2457-2472. doi: 10.1007/s00520-019-05256-4. Epub 2020 Feb 13. PMID: 32056010.

[20]. Kumar S, Singh RK, Patial B, Goyal S, Bhardwaj TR. Recent advances in novel heterocyclic scaffolds for the treatment of drug-resistant malaria. J Enzyme Inhib Med Chem. 2016;31(2):173-86. doi: 10.3109/14756366.2015.1016513. Epub 2015 Mar 16. PMID: 25775094.

[21]. Batista R, Silva Ade J Jr, de Oliveira AB. Plant-derived antimalarial agents: new leads and efficient phytomedicines. Part II. Non-alkaloidal natural products. Molecules. 2009 Aug 13;14(8):3037-72. doi: 10.3390/molecules14083037. PMID: 19701144; PMCID: PMC6254980.

[22]. Llanos-Cuentas A, Lacerda MVG, Hien TT, Vélez ID, Namaik-Larp C, Chu CS, Villegas MF, Val F, Monteiro WM, Brito MAM, Costa MRF, Chuquiyauri R, Casapía M, Nguyen CH, Aruachan S, Papwijitsil R, Nosten FH, Bancone G, Angus B, Duparc S, Craig G, Rousell VM, Jones SW, Hardaker E, Clover DD, Kendall L, Mohamed K, Koh GCKW, Wilches VM, Breton JJ, Green JA. Tafenoquine versus Primaquine to Prevent Relapse of Plasmodium vivax Malaria. N Engl J Med. 2019 Jan 17;380(3):229-241. doi: 10.1056/NEJMoa1802537. PMID: 30650326; PMCID: PMC6657225.

[23]. Rudrapal M, Chetia D. Endoperoxide antimalarials: development, structural diversity and pharmacodynamic aspects with reference to 1,2,4-trioxane-based structural scaffold. Drug Des DevelTher. 2016 Nov 1;10:3575-3590. doi: 10.2147/DDDT.S118116. PMID: 27843298; PMCID: PMC5098533.

[24]. Ferraz MB, Pinheiro GR, Helfenstein M, Albuquerque E, Rezende C, Roimicher L, Brandao L, Silva SC, Pinheiro GC, Atra E. Combination therapy with methotrexate and chloroquine in rheumatoid arthritis. A multicenter randomized placebo-controlled trial. Scand J Rheumatol. 1994;23(5):231-6. doi: 10.3109/03009749409103721. PMID: 7973475.

[25]. Martinez GP, Zabaleta ME, Di Giulio C, Charris JE, Mijares MR. The Role of Chloroquine and Hydroxychloroquine in Immune Regulation and Diseases. Curr Pharm Des. 2020;26(35):4467-4485. doi: 10.2174/1381612826666200707132920. PMID: 32634079.

[26]. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020 Mar;16(3):155-166. doi: 10.1038/s41584-020-0372-x. Epub 2020 Feb 7. PMID: 32034323.

[27]. Martinez GP, Zabaleta ME, Di Giulio C, Charris JE, Mijares MR. The Role of Chloroquine and Hydroxychloroquine in Immune Regulation and Diseases. Curr Pharm Des. 2020;26(35):4467-4485. doi: 10.2174/1381612826666200707132920. PMID: 32634079.

[28]. Millard C, Kadam AB, Mahajan R, Pollock AM, Brhlikova P. Availability of brands of six essential medicines in 124 pharmacies in Maharashtra. J Glob Health. 2018 Jun;8(1):010402. doi: 10.7189/jogh.08.010402. PMID: 29423188; PMCID: PMC5782832.

[29]. Samudrala PK, Kumar P, Choudhary K, Thakur N, Wadekar GS, Dayaramani R, Agrawal M, Alexander A. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020 Sep 15;883:173375. doi: 10.1016/j.ejphar.2020.173375. Epub 2020 Jul 17. PMID: 32682788; PMCID: PMC7366121.

[30]. Samudrala PK, Kumar P, Choudhary K, Thakur N, Wadekar GS, Dayaramani R, Agrawal M, Alexander A. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020 Sep 15;883:173375. doi: 10.1016/j.ejphar.2020.173375. Epub 2020 Jul 17. PMID: 32682788; PMCID: PMC7366121.

[31]. National Center for Biotechnology Information. "PubChem Compound Summary for CID3652,Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020 Mar;16(3):155-166. doi: 10.1038/s41584-020-0372-x. Epub 2020 Feb 7. PMID: 32034323.

[32]. Hydroxychloroquine" *PubChem*, https://pubchem.ncbi.nlm.nih.gov/compound/Hydroxychloroquine Accessed 2 July, 2022.

[33]. Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). Expert Opin Drug Saf. 2017 Mar;16(3):411-419. doi: 10.1080/14740338.2017.1269168. Epub 2016 Dec 14. PMID: 27927040.

[34]. Bansal P, Goyal A, Cusick A 4th, Lahan S, Dhaliwal HS, Bhyan P, Bhattad PB, Aslam F, Ranka S, Dalia T, Chhabra L, Sanghavi D, Sonani B, Davis JM 3rd. Hydroxychloroquine: a comprehensive review and its controversial role in coronavirus disease 2019. Ann Med. 2021 Dec;53(1):117-134. doi: 10.1080/07853890.2020.1839959. PMID: 33095083; PMCID: PMC7880079.

[35]. Van Eaton KM, Gustafson DL. Pharmacokinetic and Pharmacodynamic Assessment of Hydroxychloroquine in Breast Cancer. J Pharmacol Exp Ther. 2021 Dec;379(3):331-342. doi: 10.1124/jpet.121.000730. Epub 2021 Sep 9. PMID: 34503992.

[36]. Thakor P, Bhavana V, Sharma R, Srivastava S, Singh SB, Mehra NK. Polymer-drug conjugates: recent advances and future perspectives. Drug Discov Today. 2020 Sep;25(9):1718-1726. doi: 10.1016/j.drudis.2020.06.028. Epub 2020 Jul 3. PMID: 32629170.

[37]. Ogueri KS, Ogueri KS, Ude CC, Allcock HR, Laurencin CT. Biomedical applications of polyphosphazenes. Med Devices Sens. 2020 Dec;3(6):e10113. doi: 10.1002/mds3.10113. Epub 2020 Aug 2. PMID: 33889811; PMCID: PMC8059710.

[38]. Weikel AL, Owens SG, Morozowich NL, Deng M, Nair LS, Laurencin CT, Allcock HR. Miscibility of choline-substituted polyphosphazenes with PLGA and osteoblast activity on resulting blends. Biomaterials. 2010 Nov;31(33):8507-15. doi: 10.1016/j.biomaterials.2010.07.094. Epub 2010 Aug 25. PMID: 20800277.

[39]. Hackl CM, Schoenhacker-Alte B, Klose MHM, Henke H, Legina MS, Jakupec MA, Berger W, Keppler BK, Brüggemann O, Teasdale I, Heffeter P, Kandioller W. Synthesis and in vivo anticancer evaluation of poly(organo)phosphazene-based metallodrug conjugates. Dalton Trans. 2017 Sep 28;46(36):12114-12124. doi: 10.1039/c7dt01767g. Epub 2017 Sep 1. PMID: 28862707.

[40]. Payne LG, Andrianov AK. Protein release from polyphosphazene matrices. Adv Drug Deliv Rev. 1998 May 4;31(3):185-196. doi: 10.1016/s0169-409x(97)00122-1. PMID: 10837625.

[41]. Iviglia G, Kargozar S, Baino F. Biomaterials, Current Strategies, and Novel Nano-Technological Approaches for Periodontal Regeneration. J FunctBiomater. 2019 Jan 2;10(1):3. doi: 10.3390/jfb10010003. PMID: 30609698; PMCID: PMC6463184.

[42]. Perche F, Yi Y, Hespel L, Mi P, Dirisala A, Cabral H, Miyata K, Kataoka K. Hydroxychloroquine-conjugated gold nanoparticles for improved siRNA activity. Biomaterials. 2016 Jun;90:62-71. doi: 10.1016/j.biomaterials.2016.02.027. Epub 2016 Mar 5. PMID: 26986857.

[43]. Akpa PA, Ugwuoke JA, Attama AA, Ugwu CN, Ezeibe EN, Momoh MA, Echezona AC, Kenechukwu FC. Improved antimalarial activity of caprol-based nanostructured lipid carriers encapsulating artemether-lumefantrine for oral administration. Afr Health Sci. 2020 Dec;20(4):1679-1697. doi: 10.4314/ahs.v20i4.20. PMID: 34394228; PMCID: PMC8351851.

[44]. Parashar D, Aditya NP, Murthy RS. Development of artemether and lumefantrine co-loaded nanostructured lipid carriers: physicochemical characterization and in vivo antimalarial activity. Drug Deliv. 2016;23(1):123-9. doi: 10.3109/10717544.2014.905883. Epub 2014 Apr 30. PMID: 24786480.

[45]. Parashar D, Aditya NP, Murthy RS. Development of artemether and lumefantrine co-loaded nanostructured lipid carriers: physicochemical characterization and in vivo antimalarial activity. Drug Deliv. 2016;23(1):123-9. doi: 10.3109/10717544.2014.905883. Epub 2014 Apr 30. PMID: 24786480.

[46]. Rezaei S, Kashanian S, Bahrami Y, Zhaleh H, Cruz LJ. Enhanced Intracellular Delivery of Curcumin by Chitosan-Lipoic Acid as Reduction-Responsive Nanoparticles. Curr Pharm Biotechnol. 2021;22(5):622-635. doi: 10.2174/1389201021999200727153513. PMID: 32720599.

[47]. Dhandapani RK, Gurusamy D, Palli SR. Development of Catechin, Poly-l-lysine, and Double-Stranded RNA Nanoparticles. ACS Appl Bio Mater. 2021 May 17;4(5):4310-4318. doi: 10.1021/acsabm.1c00109. Epub 2021 May 4. PMID: 35006843.

[48]. Idris A, Davis A, Supramaniam A, Acharya D, Kelly G, Tayyar Y, West N, Zhang P, McMillan CLD, Soemardy C, Ray R, O'Meally D, Scott TA, McMillan NAJ, Morris KV. A SARS-CoV-2 targeted siRNA-nanoparticle therapy for COVID-19. Mol Ther. 2021 Jul 7;29(7):2219-2226. doi: 10.1016/j.ymthe.2021.05.004. Epub 2021 May 14. PMID: 33992805; PMCID: PMC8118699.

[49]. Nezhad-Mokhtari P, Ghorbani M, Abdyazdani N. Reinforcement of hydrogel scaffold using oxidized-guar gum incorporated with curcumin-loaded zein nanoparticles to improve biological performance. Int J BiolMacromol. 2021 Jan 15;167:59-65. doi: 10.1016/j.ijbiomac.2020.11.103. Epub 2020 Nov 16. PMID: 33212103.

[50]. Fan Y, Marioli M, Zhang K. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. J Pharm Biomed Anal. 2021 Jan 5;192:113642. doi: 10.1016/j.jpba.2020.113642. Epub 2020 Sep 19. PMID: 33011580.

[51]. Li R, Ng TSC, Wang SJ, Prytyskach M, Rodell CB, Mikula H, Kohler RH, Garlin MA, Lauffenburger DA, Parangi S, Dinulescu DM, Bardeesy N, Weissleder R, Miller MA. Therapeutically reprogrammed nutrient signalling enhances nanoparticulate albumin bound drug uptake and efficacy in KRAS-mutant cancer. Nat Nanotechnol. 2021 Jul;16(7):830-839. doi: 10.1038/s41565-021-00897-1. Epub 2021 May 6. PMID: 33958764; PMCID: PMC8491539.

[52]. de Jesús Valle MJ, Maderuelo Martín C, ZarzueloCastañeda A, Sánchez Navarro A. Albumin micro/nanoparticles entrapping liposomes for itraconazole green formulation. Eur J Pharm Sci. 2017 Aug 30;106:159-165. doi: 10.1016/j.ejps.2017.05.066. Epub 2017 Jun 1. PMID: 28577996.

[53]. Klionsky DJ, Abdel-Aziz AK, et. al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)[1]. Autophagy. 2021 Jan;17(1):1-382. doi: 10.1080/15548627.2020.1797280. Epub 2021 Feb 8. PMID: 33634751; PMCID: PMC7996087.

[54]. Ahmad AM, Mohammed HA, Faris TM, Hassan AS, Mohamed HB, El Dosoky MI, Aboubakr EM. Nano-Structured Lipid Carrier-Based Oral Glutathione Formulation Mediates Renoprotection against Cyclophosphamide-Induced Nephrotoxicity, and Improves Oral Bioavailability of Glutathione Confirmed through RP-HPLC Micellar Liquid Chromatography. Molecules. 2021 Dec 10;26(24):7491. doi: 10.3390/molecules26247491. PMID: 34946570; PMCID: PMC8706828.

[55]. Karthik L, Kumar G, Keswani T, Bhattacharyya A, Reddy BP, Rao KV. Marine actinobacterial mediated gold nanoparticles synthesis and their antimalarial activity. Nanomedicine. 2013 Oct;9(7):951-60. doi: 10.1016/j.nano.2013.02.002. Epub 2013 Feb 19. PMID: 23434675.

[56]. Ashrafi Z, Lucia L, Krause W. Underwater Superoleophobic Matrix-Formatted Liquid-Infused Porous Biomembranes for Extremely Efficient Deconstitution of Nanoemulsions. ACS Appl Mater Interfaces. 2020 Nov 11;12(45):50996-51006. doi: 10.1021/acsami.0c13718. Epub 2020 Oct 29. PMID: 33119268.

[57]. Sultana N, Wang M. Fabrication of HA/PHBV composite scaffolds through the emulsion freezing/freeze-drying process and characterisation of the scaffolds. J Mater Sci Mater Med. 2008 Jul;19(7):2555-61. doi: 10.1007/s10856-007-3214-3. Epub 2007 Aug 1. PMID: 17665100.

[58]. Mousavi SM, Hashemi SA, Ghasemi Y, Atapour A, Amani AM, SavarDashtaki A, Babapoor A, Arjmand O. Green synthesis of silver nanoparticles toward bio and medical applications: review study. Artif Cells NanomedBiotechnol. 2018;46(sup3):S855-S872. doi: 10.1080/21691401.2018.1517769. Epub 2018 Oct 17. PMID: 30328732.

[59]. Akter M, AtiqueUllah AKM, Banik S, Sikder MT, Hosokawa T, Saito T, Kurasaki M. Green Synthesized Silver Nanoparticles-Mediated Cytotoxic Effect in Colorectal Cancer Cells: NF-κB Signal Induced

Apoptosis Through Autophagy. Biol Trace Elem Res. 2021 Sep;199(9):3272-3286. doi: 10.1007/s12011-020-02463-7. Epub 2020 Nov 24. PMID: 33236292.

[60]. Minopoli A, Della Ventura B, Campanile R, Tanner JA, Offenhäusser A, Mayer D, Velotta R. Randomly positioned gold nanoparticles as fluorescence enhancers in apta-immunosensor for malaria test. MikrochimActa. 2021 Feb 16;188(3):88. doi: 10.1007/s00604-021-04746-9. PMID: 33594523; PMCID: PMC7886758.

[61]. Kumar R, Ray PC, Datta D, Bansal GP, Angov E, Kumar N. Nanovaccines for malaria using Plasmodium falciparum antigen Pfs25 attached gold nanoparticles. Vaccine. 2015 Sep 22;33(39):5064-71. doi: 10.1016/j.vaccine.2015.08.025. Epub 2015 Aug 20. PMID: 26299750; PMCID: PMC4577455.

[62]. Surolia R, Pachauri M, Ghosh PC. Preparation and characterization of monensin loaded PLGA nanoparticles: in vitro anti-malarial activity against Plasmodium falciparum. J Biomed Nanotechnol. 2012 Feb;8(1):172-81. doi: 10.1166/jbn.2012.1366. PMID: 22515105.

[63]. Ponarulselvam S, Panneerselvam C, Murugan K, Aarthi N, Kalimuthu K, Thangamani S. Synthesis of silver nanoparticles using leaves of Catharanthus roseus Linn. G. Don and their antiplasmodial activities. Asian Pac J Trop Biomed. 2012 Jul;2(7):574-80. doi: 10.1016/S2221-1691(12)60100-2. PMID: 23569974; PMCID: PMC3609350.

[64]. Mulik RS, Mönkkönen J, Juvonen RO, Mahadik KR, Paradkar AR. Apoptosis-induced anticancer effect of transferrin-conjugated solid lipid nanoparticles of curcumin. Cancer Nanotechnol. 2012;3(1-6):65-81. doi: 10.1007/s12645-012-0031-2. Epub 2012 Nov 13. PMID: 26069496; PMCID: PMC4452039.