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Antimalarial Drugs and COVID -19

Modupe Iretiola Builders*
Department of Pharmacology and Toxicolology, Faculty of Pharmaceutical Sciences, Nasarawa State, Nigeria
Email: modupebuilders@yahoo.com

Joseph Oyepata Simeon
Department of Pharmacology and Toxicolology, Faculty of Pharmaceutical Sciences, Nasarawa State, Nigeria

Timothy Olugbenga Ogundeko
Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, Bingham University, Jos Campus, Nigeria. Nasarawa State, Nigeria

Philip Builders
Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development, Abuja, Nigeria

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Abstract
The coronavirus disease 2019 (COVID-19) is a novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that is ravaging the world. Therefore, the need to find new preventive and therapeutic drug at the earliest possible time additionally to the implementation of preventive measures such as early detection, isolation and treatment of cases as well as minimization of transmission through physical interaction. Moreover, specific vaccines and yet effective treatment that target the 2019. This review focuses on the use of antimalarial drugs as therapeutics interventions for COVID-19.
Keywords: COVID-19; SARS-CoV-2; Malaria; Antimalarial drugs.

1. Introduction
In December 2019, the coronavirus infection arose from Wuhan and transformed into a global calamity [1]. The virus is known as severe acute respiratory syndromecoronavirus-2 (SARS-CoV-2) and the causative agent of the infection is called coronavirus disease 2019 (COVID-19) [2]. SARS-Cov-2 belong to the family of betacoronavirus , this includes already common viruses, Middle East respiratory syndrome (MERS) (2012) de Groot, *et al.* [3] and Xiao, *et al.* [4]. It is considered to be a bat virus; but, its intermediate host during transmission to humans is not proven [5].

1.1. SARS-CoV-2
SARS-CoV-2 occurs as a positive sense single-strand RNA virus with a genome size of approximately 30,000 nucleotides and is made up of proteins such as spikes, envelope, nucleocapsid, matrix, RNA-dependent RNA polymerase, and proteases [6]. Several studies on SARS-CoV revealed that spike protein subunits mediated the interaction between angiotensin converting enzyme 2 (ACE2) host cell receptor and SARS-CoV [7].

2. COVID-19
Coronavirus disease (COVID-19) is an infectious disease caused by a novel coronavirus. Coronaviruses are associated with gastrointestinal disease in humans, poultry, and bovines. A species known as SARS coronavirus causes a highly contagious respiratory disease in humans, that is characterized by symptoms of fever, cough, and muscle ache, often with progressive difficulty in breathing [8, 9]. The elderly and those with comorbidities may develop pneumonia, acute respiratory distress syndrome and organ dysfunction [10]. They cause respiratory tract infections ranging from mild to lethal, some cases of the common cold may result to mild illnesses in humans (which is also caused by other viruses, predominantly rhinoviruses), while more fatal forms can cause SARS, MERS, and COVID-19 [9].

COVID-19 pandemic is a fast and prevalent outbreak of a novel coronavirus caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [11, 12]. The World Health Organization confirmed the outbreak a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March. As of 17 September 2020, more than 29.9 million cases have been reported in 188 countries and territories, resulting in more than 942,000 deaths; more than 20.3 million people have recovered [13].

The COVID-19 virus is transmitted mainly through droplets of saliva or discharge from the nose when an infected person coughs or sneezes and also through suspended larger droplets in air such as aerosols, especially in indoor spaces. It may also spread via contaminated surfaces, although this has not been scientifically established [9].

*Corresponding Author

Preventive measures from persons to persons include (1) using face masks; (2) covering coughs and sneezes with tissues; (3) washing hands regularly with soap or disinfecting with sanitizers containing at least 60% alcohol; (4) avoiding contact with infected people; (5) maintaining a physical distance between people (1.5 m), and (6) refraining from touching eyes, nose, and mouth with unwashed hands [14].

3. Malaria

Malaria is the most important tropical parasitic disease caused by protozoan parasites of the genus Plasmodium, transmitted by mosquitoes of the genus Anopheles. More than two billion people, nearly 40% of the world's population are at risk [15]. It is a public health problem of global concern because of its high economic burden on the nation, high prevalence of mortality in children, pregnant women and non-immune individuals [16]. Malaria is also directly responsible for 20% of childhood deaths in Africa and leading cause of mortality in Nigeria where it is holo-endemic. Malaria is a leading cause of morbidity and mortality among children in sub-Saharan Africa [15, 16].

3.1. Malaria and COVID- 19

The healthcare systems in both low and middle -income countries are already fragile as a result of weak infrastructures, shortage of health workers, and limited financial resources. Thus, it is very pertinent to put some measures in place to prevent indirect short- and long-term effects of the COVID-19 pandemic [17] on malaria control programs and on healthcare systems of countries where the two diseases can coexist. This will go a long way in overcoming the consequences of the two infections. Studies on the association between malaria and COVID -19 is scarce, the figures below indicate the global epidemiology of COVID-19 and Africa epidemiology of COVID-19 on August 17, 2020 [18].

Figure-1.

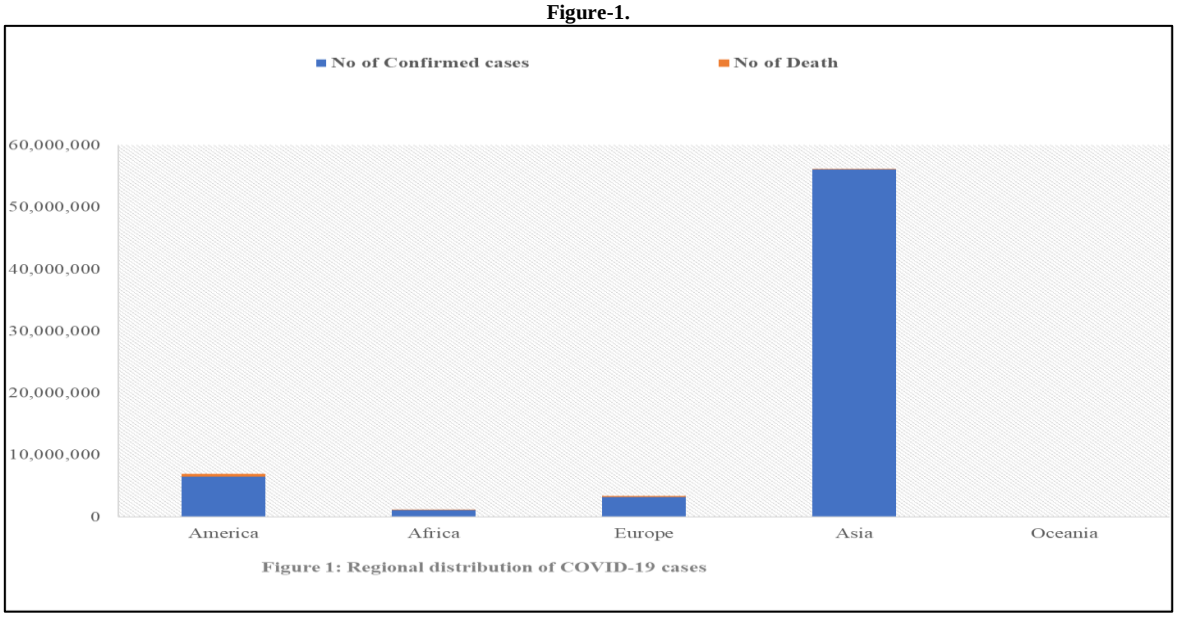


Figure 1: Regional distribution of COVID-19 cases

Figure-2.

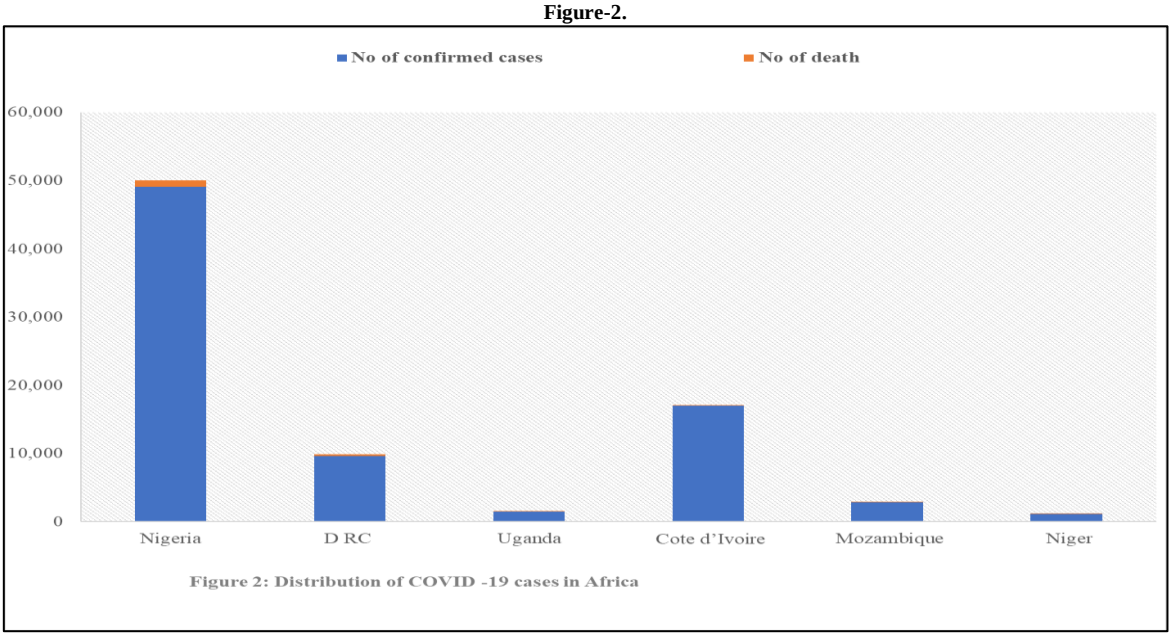


Figure 2: Distribution of COVID -19 cases in Africa

3.2. Antimalarial Drugs

Presently, there are no proven drug therapy for the treatment of COVID 19. However, some antimalarial drugs have been documented as future drugs for the treatment of COVID 19. Verifiable treatment with remodel antimalarial drugs such as chloroquine, hydroxychloroquine, azithromycin, pyronaridine and Artemisinin- based combination therapy (ACT) is going on [19].

4. Amoniquinoline

Chloroquine was until recently the most widely used antimalarial. It was the original prototype from which most other methods of treatment are derived including hydroxychloroquine [20]. Hydroxychloroquine is more potent than chloroquine with less side effects and they both belong to 4-aminoquinoline with similar pharmacological properties [1].

Amodiaquine is most frequently used in combination with chloroquine, but is also very effective when used alone. It is thought to be more effective in clearing parasites in uncomplicated malaria than chloroquine, thus leading to a faster rate of recovery. But, its usage in chemoprophylaxis is reduced due to some fatal adverse effects. The WHO, s most recent advice on the subject still maintains that the drug should be used when the potential risk of not treating an infection outweighs the risk of developing side effects. It has been suggested that it is particularly effective, and less toxic than other combination treatments in HIV positive patients [20]

In vitro and pre-clinical studies indicated that the two drugs have some efficiency in lowering viral replication SARS-COV and SARS-COV -2. However, hydroxychloroquine was found to be more effective than chloroquine in reducing SARS-COV-2 in vitro [21]. The anti-inflammatory activities of these drugs have also been reported by several authors, they interfere the Angiotensin Converting Enzyme (ACE2) cell receptor and are also active against many proinflammatory cytokines such as IL-1 and IL-6 [1, 18]. The in-vitro study of Chloroquine or Hydroxychloroqine with an antibiotic (Azithromycin) against SARS-COV -2 is still ongoing [18, 21].

4.1. Artemisinin Derivatives

The popularly used chloroquine (CQ) has been associated with treatment failure due to drug resistant strains of P. falciparum found in many endemic areas of the world. In order to eliminate the evolution of resistance acquired by malaria parasites, the need to develop newer drug regimen [22]. A plant-based antimalarial drug was isolated from the Chinese plant Artemisia annua in seventies, World Health Organization recommended the use of artemisin in based combination therapy (ACT) as first line therapy for the treatment of uncomplicated malaria to increase the goal of treatment and prevent emergence of resistance to therapy [19, 20, 22]. Artemisinin derivatives have very short half-lives, thus using them as monotherapy requires doses over a period of 7 days. Combination of one of these drugs with a longer half- life partner antimalarial drug allows a reduction in the duration of antimalarial treatment while at the same time increasing efficacy and decreasing the likelihood of resistance development [20].

4.2. Artesunate

Artesunate is a hemisuccinate derivative of the active metabolite dihydroartemisinin. Presently, it is the most commonly used of all the artemisinin type drugs. Its only effect is mediated through a reduction in the gametocyte transmission. It is used in combination therapy and is effective in cases of uncomplicated P. falciparum. Several studies indicated no adverse effects in large population [20].

4.3. Dihydroartemisinin

Dihydroartemisinin is the active metabolite to which artemisinin is reduced. It inhibits the sarcoplasmic/ endoplasmic reticulum calcium ATPase encoded by P. falciparum. This is the most effective artemisinin compound and the least stable. It has a strong blood schizonticidal action and decreases gametocyte transmission. It is used for therapeutic treatment of cases of resistant and uncomplicated P.falciparum [20].

4.4. Mefloquine

Mefloquine is now solely used for the prevention of resistant strains of P. falciparum despite being effective against P. vivax, P. ovale, and P. malariae. Mefloquine is effective in prophylaxis and for acute therapy. It is now strictly used for resistant strains (and is usually combined) [20].

4.5. ACT

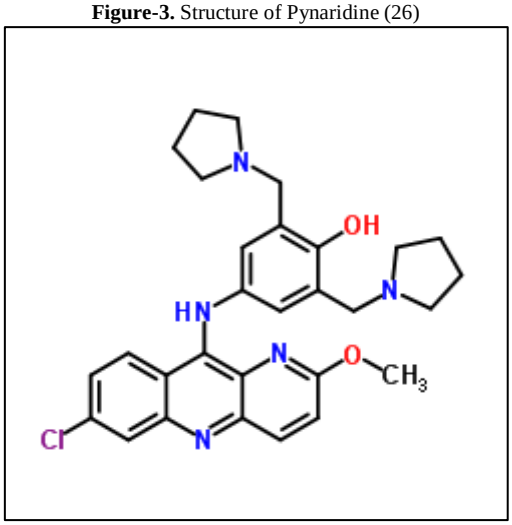
ACT is a combination therapy of antimalarial drug with artemisinin derivative as one component of the combination. It can be a fixed combination of medicinal product in which the components are co-administered in separate tablet or capsule, for example Mefloquine and dihydroartemisinin. The combination therapy is easier to use, motivates better compliance and reduces the potential use of components of the combination as therapy [20].

In vitro activity of ACT against t SARS-CoV-2 sequel to oral administration of ACT for uncomplicated malaria treatment has been documented [19]. Also, artemisinin has shown anti-inflammatory effects as well as inhibition of interleukin-6 (IL-6) that serves critical function in the development of severe coronavirus disease 2019 (COVID-19) [25]. Mefloquine–artesunate, another type of ACT has also indicated potent antiviral activity against SARSCoV-2 with enhanced drug concentration in lung tissue, a possible clinical advantage in COVID-19 [25] as highlighted in table 1.

4.6. Pyronaridine

An antimalarial dosage form (Pyronaridine), a combination of mepacrine and amodiaquine shown in figure 4 made in 1970 at the Institute of Chinese Parasitic Disease was used to treat chloroquine-resistant *Plasmodium falciparum* infections. Association of Pyronaridine with Artesunate which serves as ACT is used for treating multidrug -resistant infections [23]. In vitro comparism study of pyronaridine, artesunate, and hydroxychloroquine effectiveness against SARSCOV-2 reveal that pyronaridine and artesunate are more effective than hydroxychloroquine in the human lung epithelial cell line Calu-3 [23] as illustrated in table 1.

Figure-3. Structure of Pynaridine (26)



4.7. Piperaquine

Piperaquine was first manufactured in China in the 1960s and has been widely used in China and other countries ever since. It is similar to chloroquine by possessing bisquinoline group [21] as shown in figure 4.

Figure-4. Structure of Piperaquine (27)

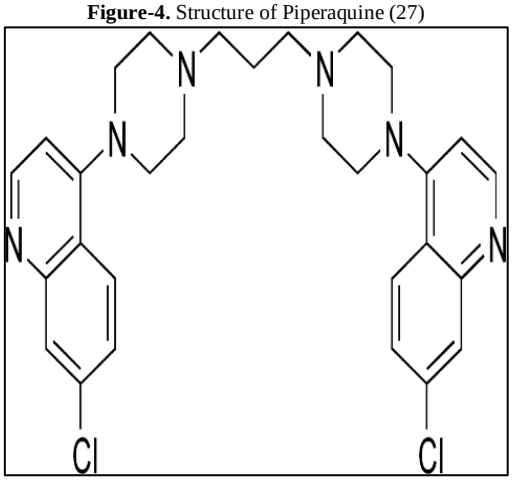


Table-1. I*n vitro* activity of some antimalarial drugs against SARS-Cov-2 [19, 23]

ANTIMALARIALS	CELL LINE	INHIBITION (%)	IC_{50} (µM)
Pyronaridine	Vero	-	1.1
Hydroxychloroquine	Vero	-	1.1
Artesunate	Vero	-	53
Mefloquine-Dihydroartemisinin	Vero	99.6	1-10
Desethylamodiaquine–hydroartemisinin	Vero	85.8	1-10
Pyronaridine-Dihydroartemisinin	Vero	38.2	1-10
Lumefantrine-Dihydroartemisinin	Vero	37.7	1-10
Piperaquine-Dihydroartemisinin	Vero	29.7	1-10

4.8. Miscellaneous

Doxycycline is a tetracycline compound obtained from oxytetracycline. It was one of the earliest groups of antibiotics to be developed and is still used widely in many types of infection. Doxycycline is used essentially for chemoprophylaxis in areas where resistance exists. It can be used in resistant cases of uncomplicated P.falciparum, however a very slow action in acute malaria. Therefore, it is not recommended for monotherapy [20]. Halofantrine is not commonly used for prophylaxis or treatment of malaria due to its high cost. It has very variable bioavailability and has been shown to have potentially high levels of cardio toxicity. It is still a useful drug and can be used in

patients that are known to be free of heart disease and are suffering from severe malaria [20]. Mefloquine is now solely used for the prevention of resistant strains of P. falciparum despite being effective against P. vivax, P. ovale, and P. malariae. Mefloquine is effective in prophylaxis and for acute therapy. It is now strictly used for resistant strains (and is usually combined with artesunate) [20].

4.9. Docking of Antimalarial Drugs

Studies have shown that COVID-19 is as a result of interactions between viral spike proteins and ACE2, since spike protein is essential in the viral attachment and entry [24]. Thus, these interactions can be target for the development of drugs and vaccines by blocking the interactions. Also, the main protease, MPro, is an essential enzyme that plays important role for polyprotein or polypeptide processing, therefore viral replication can also be blocked by blocking the activity of main protease [25].

The in-silico potential of several antimalarial drugs for repurposing against COVID-19 has been reported, the antimalarial compounds were docked against two SARS-CoV-2–specific targets: the receptor binding domain spike protein and the main protease of the virus (MPro) using the Schro¨dinger software [5]. Doxycycline (DOX) exhibited the most effective binding to the spike protein of SARS-CoV-2, whereas halofantrine and mefloquine bound effectively with the main protease among the antimalarial drugs evaluated in the docking analysis [5] as indicated in table 2.

Table-2. Docking parameters of antimalarial drugs with receptor binding domain spike protein [5]

ANTIMALARIAL	GSCORE		DSCORE		Emodel	
DRUGS	**6M0J**	**6YLA**	**6M0J**	**6YLA**	**6M0J**	**6YLA**
Amodiaquine	-3.55	-3.88	-2.94	-3.27	-43.89	-59.58
Chloroquine	-4.02	-3.97	-3.98	-3.93	-36.97	-42.63
Doxycycline	-7.09	-5.20	-4.57	-4.98	-49.70	-45.42
Halofantrine	-3.96	-3.92	-3.96	-3.96	-59.96	-40.44
Hydroxychloroquine	-6.23	-4.74	-3.99	-4.69	-46.11	-43.72
Lumefantrine	-4.95	-2.66	-3.05	-0.76	-66.74	-46.92
Mefloquine	-4.30	-3.14	-4.29	-3.13	-43.15	-45.30

5. Conclusion

Malaria and Covid-19 may have similar characteristics and correlations. For example, in this documentation, we found out that Africa countries that commonly use ACT report fewer cases and deaths during malaria season which also correlate with COVID-19 cases. Several studies have shown the antiviral activity and anti-inflammatory activity of ACT against SARS-CoV-2 as well as therapeutic potential of doxycycline and halofantrine against COVID-19 infection. Therefore, it is recommended that these antimalarials should be evaluated clinically to treat COVID-19 and if possible, combination therapy for better clinical efficacy.

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