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Pollution of environment by Chloroquine as treatment of COVID-19

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Abstract

COVID-19 has spread as a pandemic public health concern. Until now, many people have searched for remedies to prevent or treat the disease of the pandemic COVID-19. Due to the rapid emergence of the pandemic in all geographic, unavailable of vaccine, clinical presentation and specific diagnostic tests imaginable challenges are proposed to combat this epidemic. Hydroxychloroquine and similar medication called Chloroquine was recommended as a treatment protocol of COVID-19 pandemic until a vaccine for COVID-19 is available but since chloroquine (CQ) and hydroxychloroquine (HCQ) and its metabolites reach wastewater treatment plant and environment where its occurrence is a source of pollution. As result, hydroxychloroquine was certainly fates of large quantities via wastewaters contaminated the environment and are identified as potentially persistent and bioaccumulative, behavior in the environment. Both chloroquine and hydroxychloroquine posed serious chronic threat to the aquatic organism. This is highly relevant since it is known that wastewater treatment systems do not have adequate processes for treatment these drugs, which will enter into freshwater ecosystems. Hence, inadequate water treatment plants and worse implementation of methodologies that contribute to decrease/elimination of these pharmaceuticals from water and wastewater is considered as high potential for being the next emerging pharmaceutical contaminant in World.

1. Introduction

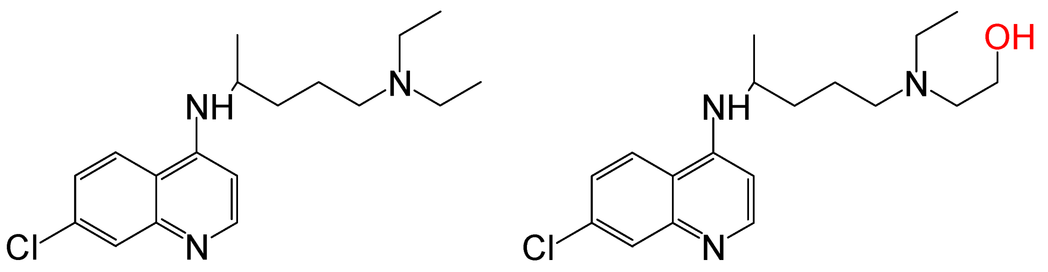
Every year, the production of pharmaceutical product for human have been expanding in Worldwide (OECD, 2018), also, more development is anticipated in future. After use, their disposal unmetabolized are excreted by humans and due to their incomplete elimination in wastewater, a large amount of drugs have been discharged into the environment. Frequently, they are detected in aquatic environments worldwide, both in the water and in aquatic organisms [1][2]. However, Due to their lipophilic property and their resistance to degradation, they persist in the aquatic environment where they present a serious issue throughout the world and have negative effects on the biota [3].

Recently, in 2020 a new virus knows as SARS-CoV-2 (Coronavirus) invades and emerges the world via a widespread human transmission [4]. Since, December 2019, the spread of Pandemic COVID-19 in worldwide [5] as an infectious disease, it’s occurs after infecting a human with severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) (ARDS). On January 31, 2020, COVID-19 as a Public Health Emergency of International Concern (PHEIC), was declared by (WHO), however, that it can pose a menace to many countries and needs an urgent, coordinated international response [6]. On 11th March 2020, the WHO [7] announced that the COVID-19 outbreak as a "pandemic public health menace." For this, the necessity for early detection, quarantine, and rapid treatment was proposed by the global emergency committee [8].

Thus, many existing drugs such as the anti-malarial drugs Chloroquine (CQ) [9] and Hydroxychloroquine (HCQ) (Plaquenil, among others) (Science News, 2020) are re-purposed in the latest version of the "Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-Induced Pneumonia," issued by the National Health Commission of the People's Republic of China [10] as a treatment protocol for COVID-19 until an antidote for COVID-19 is available.

Since the 1930s, CQ has been used as a primary antimalarial drug due to its tolerability, effectiveness and inexpensive synthesis [11], also as an antifungal [12], treatment of rheumatic and immune-mediated diseases [13] and it is used also for the management of HIV, SARS-CoV and influenza A/H5N1 virus [14].

It is belongs the quinoline group $C_{18}H_{26}ClN_3$ as molecular formula, CQ includes derivate products as like chloroquine phosphate ($C_{18}H_{29}ClN_3.H_3PO_4$), chloroquine diphosphate ($C_{18}H_{29}ClN_3.2H_3PO_4$), chloroquine sulfate ($C_{18}H_{26}ClN_3$. H_2SO_4) and chloroquine dihydrochloride ($C_{18}H_{26}ClN_3.2HCl$) [15]. Also, recently, research in the laboratory and in-vivo studies revealed that the chloroquine and hydroxychloroquine (Scheme 1) were highly effective against COVID-19 [7]. But, Overproduction and overuse use of CQ and HCQ during the COVID-19 pandemic has increased and they may enter the aquatic ecosystem via wastewater effluents, washing out of fecal materials by rain, domestic wastewater and STPs [42].



Chloroquine (CQ)
CAS No. 54-05-7
Formula: $C_{18}H_{26}ClN_3$
MW: 319.9

Hydroxychloroquine (HCQ)
CAS No. 118-42-3
Formula: $C_{18}H_{26}ClN_3O$
MW: 335.9

Scheme 1: Chloroquine and hydroxychloroquine molecules

Fate of Chloroquine and Hydroxychloroquine in wastewater

The derivatives of Quinoline: Chloroquine and quinine are used as Malaria treatment, also they have used in other medical applications widely in Asia, Africa and South America [16][17]. Substantial portion of Hydroxychloroquine excreted unchanged [18]. As a result, unchanged or metabolized form discharged from bodies (40–60%) mainly through kidney and (8–25%) from feces as quinine unaltered or as 3-hydroxyquinine and N-desethyl chloroquine [19][20].

Hospital wastewater as one source of high concentration of these drugs, and due to abusive use, one would expect that their levels and diversity have increased during the COVID-19 pandemic [21][22][23].

CQ and its metabolites reach into the environment where its fate and behavior due to their physicochemical properties, it can be discharged via wastewater treatment plants. A series of treatment processes at the wastewater treatment plants (WWTPs), are used to eliminate these compounds but due to inadequate treatment, these drugs enter into the aquatic environment. 0% degradation in 28 days of Hydroxychloroquine showed via the biotic degradation test [24]. Some literature, reported the photodegradation of hydroxychloroquine in aquatic environment and is pH-dependent, being higher under alkaline than acidic pH condition [43]. Consequently, All these sums up to the possibility of achieving 80% removal efficiency predicted for (hydroxy) chloroquine in WWTPs [44].

So, Hydroxychloroquine is potentially persistent and bioaccumulate [25]. However, due to the large production of HCQ and its potentiality of persistence and bioaccumulation, it has the high potential for being the next emerging pharmaceutical contaminant [18][26]. Although, these drugs have ability to be persistent, bioaccumulate and toxic to aquatic organisms [27]. This is highly relevant since it is known that wastewater treatment systems due to inadequate processes for treatment these drugs used by people who are infecting by viral infection [45] [46], which will enter into freshwater ecosystems [28] (figure 1).

Despite the limited Knowledge on the fate of antimalarial drug residuals in the environment, some studies detected these drug residuals in many bodies. However, little research reports the disposal and elimination of Chloroquine in water. Most studies on Hydroxychloroquine, meanwhile, focus on the stability of the compound and its metabolites in water [45]. Even so, recently, Chloroquine was detected in wastewater where a concentration of of 857 ng L was detected [44]. In addition, the predicted concentration of Chloroquine during the pandemic of COVID-19 in the surface water is over 32 ng/L [44]. Although, the result of Chen [32], in southeast China, which detected in surface sediment from tidal sections of the river residues of HCQ.

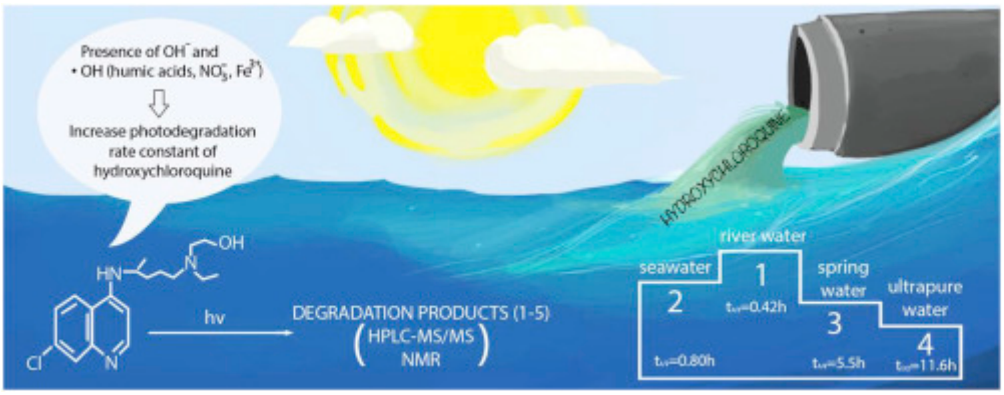


Figure 1: Fate of Hydroxychloroquine in water bodies.[29]

Also, chloroquine is likely to be absorbed by soil, however, a monitoring study of Miyai [33]. In Japan reported that the antimalarial drugs such as Chloroquine, Artesunate, Quinine, and Doxycline are detected in a pharmaceutically polluted agricultural soil, their chlorinate carbon groups indicate some persistence. Although, high concentrations of Chloroquine are toxic, to soybean and reduce the protozoa population of soil microbiota [34]. However, the Hydroxychloroquine was one of the drugs for which the highest growth during 2020, in contrast to the same period in 2019 [46]. So, the same approach was employed to estimate concentrations of this drug in surface water which was 78.3 ng /L and 833 ng/L in domestic wastewater [44].

Ecotoxicity of Chloroquine and Hydroxychloroquine

These drugs belong to a group of quinolone derivatives; both chloroquine and hydroxychloroquine posed serious chronic threat to the aquatic environment. So, these drugs are recalcitrant, persistent, toxic, carcinogenic and teratogenic in nature. Predicted No Effect Concentration (PNEC) was PEC/PNEC ≤ 0.1: the use of HCQ has been considered to result in insignificant environmental risk. But, the study of [44] predicted the environmental concentrations (PEC) in influent wastewater, secondary effluent and downstream river water. So, Both drugs are reported to pose adverse health risks to aquatic organisms.

The expose of some species of fish cells *Poeciliopsis lucida* and microorganism as *Daphnia magna, Chlorella vulgaris* and the bacterium *Vibrio fischeri* to CQ for 48h, the median effective concentration (EC50) was 9, 27, 43 and 126 mg/L respectively [35]. However, the result of *Zurita* [35] using the bioassays of invertebrate *Daphnia magna* and alga *Chlorella vulgaris* suggested that chloroquine may be harmful to aquatic organisms [35]. In addition of binding of CQ with DNA and inhibits the metabolic functions, interfere with haemoglobin, it causes also cell mediated death [13].

As same as the findings of MacPhee and Ruelle [36] observed that the expose of *salmon upon* to 20 µM of CQ, caused mortality of fish, whereas only behavioral changes were noticed in rainbow trout exposed to 388 µM of CQ after 24 h [37]. Also, the inhibition growth of algae (*Raphidocelis subcapitata*) by Hydroxychloroquine after a 72-h exposure was for the EC50=3.1 mg/L[47]. But, in comparaison, the groupement hydroxyl of hydroxychloroquine makes it less toxic than chloroquine, both share similar activity and reactivity [48].

Acute toxicity studies will be useful only when these pharmaceuticals are discharge [38]. (Tables 1 &2).

Table 1: Predicted No Effect Concentration (PNEC) by Protocol: OECD 201

PPAC	Test biota	EC10 72h	EC50 72h	NOEC 72h	Ref
Hydroxychloroquine	Algae (*Pseudokirchneriella subcapitata*)	1830 µg/L	3110 µg/L	768 µg/L	[39]
Hydroxychloroquine Sulfate	Algae (*Pseudokirchneriella subcapitata*)	1950 µg/L	3570 µg/L	183 µg/L	[40]

ND: not determined

Table 2: Predicted No Effect Concentration (PNEC) by Protocol: OECD 202, 211[41]

	Test biota	EC10 48 h	EC50 48 h	NOEC 48 h	Ref
Hydroxychloroquine	Crustacean (*Daphnia*	ND	14000µg/L	6760 µg/L	[39]

	magna				
	Test biota	EC10 21d	EC50 21d	NOEC 21d	
Hydroxychloroquine Sulfate	Crustacean (*Daphnia magna*	173 µg/L	ND	85.8 µg/L	[40]

ND: not determined

OECD: Organization for Economic Co-operation and Development, Guidelines for the Testing of Chemicals.

Conclusion

There is limited information available about the potential environmental effects of chloroquine (CQ), but, the presence of chloroquine and hydroxychloroquine residual drugs in the wastewater samples may constitute a significant environmental problem if allowed to persist for a while. Hence, inadequate water treatment plants and worse implementation of methodologies that contribute to decrease/elimination of these pharmaceuticals from water and wastewater is considered as high potential for being the next emerging pharmaceutical contaminant in World. So, it's very important that the Researchers must currently be looking for an effective vaccine for SARS-CoV-2 and anti-SARS-CoV-2 drugs to prevent the world against the pandemic and reduce the pollution of CHLOROQUINE.

Declarations

Not applicable' for that section.

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