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Chloroquine and hydroxychloroquine in the environment and aquatic organisms: a review

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ABSTRACT

Chloroquine and hydroxychloroquine are aminoquinolines used in the treatment of endemic diseases in Latin America such as malaria and non-endemic with wide prevalence such as rheumatoid arthritis and lupus erythematosus. Described as persistent, bioaccumulative, and dangerous for aquatic biota, chloroquine and hydroxychloroquine are considered emerging pollutants intensified by the COVID-19 pandemic, occurring in low concentrations that are not totally removed in wastewater treatment plants and are not covered by legislation. This article presents a theoretical approach based on literature review following a semi-systematic methodology covering detection strategies of the chloroquine and hydroxychloroquine drugs in effluent and receiving water bodies; estimates of environmental concentrations during the pandemic; methods that use degradation and removal of compounds from water; and toxic effects on aquatic biota. Concentrations previously detected and estimated in the aquatic environment can lead to significant changes in animal physiology analyzed from biomarker changes, behavior and mortality in studies with native and non-native species. Studies are necessary to reproduce and understand possible environmental scenarios adopting the indiscriminate use of drugs to serve as standards for environmentally safe concentrations when there is no specific legislation.

Keywords: COVID-19, emerging pollutants, toxicity.

Cloroquina e hidroxicloroquina no ambiente e organismos aquáticos: uma revisão

RESUMO

A cloroquina e a hidroxicloroquina são aminoquinolinas utilizadas no tratamento de doenças endêmicas da América Latina como a malária e não endêmicas com ampla prevalência como a artrite reumatoide e o lúpus eritematoso. Descritas como persistentes, bioacumulativas e perigosas para a biota aquática são consideradas poluentes emergentes intensificados pela pandemia de COVID-19, ocorrendo em baixas concentrações que não são totalmente removidas em estações de tratamento de efluentes e não são contempladas pela legislação. Este artigo tem

como objetivo apresentar uma abordagem teórica baseada em revisão de literatura semi-sistemática abrangendo estratégias de detecção dos fármacos cloroquina e hidroxicloroquina em efluentes e corpos d'água receptores; estimativas de concentrações ambientais durante a pandemia; métodos que utilizam a degradação e remoção dos compostos na água; e os efeitos tóxicos sobre a biota aquática. Concentrações previamente detectadas e estimadas para o ambiente aquático podem levar a alterações significativas na fisiologia animal, analisadas a partir de alterações de biomarcadores, comportamento e mortalidade em estudos com espécies nativas e não nativas. Se faz necessário pesquisas que busquem reproduzir e compreender possíveis cenários ambientais com o uso indiscriminado dos medicamentos para servir como padrões de concentrações ambientalmente seguras na ausência de uma legislação específica.

Palavras-chave: COVID-19, poluentes emergentes, toxicidade.

1. INTRODUCTION

Chloroquine (CQ) belongs to the quinoline group, known for its bactericidal, antiseptic, and antipyretic actions (Ramesh *et al.*, 2018). The drug has been used to treat malaria endemic in eighteen countries in Latin America and the Caribbean and has seen an increase in estimated case incidence since 2015, where Brazil represents 20% of cases (WHO, 2020). Chloroquine has also been used for rheumatoid arthritis and lupus erythematosus (Rainsford *et al.*, 2015), non-endemic diseases that have also registered an increase in this region (Hernández-Negrín and Padilla-Cueto, 2020; Papadimitropoulos *et al.*, 2022). In recent decades its action has been explored as a broad-spectrum antiviral agent in inhibiting the replication of other respiratory viruses, such as influenza A/H5N1, SARS-CoV, and human coronavirus 229E (Savarino *et al.*, 2003; Vincent *et al.*, 2005; Kono *et al.*, 2008; Murray *et al.*, 2010; Yan *et al.*, 2013).

A derivative of chloroquine, hydroxychloroquine (HCQ), with similar action, was first synthesized in 1946 when a hydroxyl group was introduced to reduce toxicity to organisms (McChesney, 1983). However, at high concentrations or prolonged use, both can cause acute intoxication and death (Weniger, 1979; Wichmann *et al.*, 2007). This is due to the fact that both are water soluble and have good oral bioavailability, reaching high plasma levels in patients, which, added to the extremely long elimination half-life (weeks to months) and large volumes of distribution, indicates significant partitioning into tissues and organs (Davis *et al.*, 2020; Drugbank, 2022a; 2022b).

At the beginning of the COVID-19 pandemic, published in vitro studies demonstrated the effectiveness of chloroquine (Wang *et al.*, 2020) and hydroxychloroquine (Liu *et al.*, 2020; Gautret *et al.*, 2020) as drugs to be administered to combat the SARS-CoV-2 virus. Motivated by these data, the use of these drugs increased considerably, and the drugs were adopted as a treatment protocol, becoming one of the drugs for which there was the highest sales growth rate in 2020, in contrast to the same period in 2019 (Yazdany and Kim, 2020; Malik *et al.*, 2020; Nasir *et al.*, 2020; Agarwal *et al.*, 2021; Romano *et al.*, 2021), although its efficacy against SARs-CoV-2 and high toxicity to patients was questioned by several studies (Shukla *et al.*, 2020; Ghazy *et al.*, 2020; Jameleddine *et al.*, 2020; Sanders *et al.*, 2020; Rosenberg *et al.*, 2020; Geleris *et al.*, 2020; Luz *et al.*, 2021). Thus, places with a high incidence of COVID-19, together with a high rate of eliminating aminoquinolines in patients´ excretion, incorrect disposal and low removal in Wastewater Treatment Plants (WWTPs), or even in the absence of these, resulted in residual concentrations of pharmaceuticals in water bodies, causing ecotoxicological risks (Kuroda *et al.*, 2021).

Described as persistent, bioaccumulative and dangerous to aquatic biota, this can lead to adverse effects on aquatic and human life (Bila and Dezotti, 2003; Ramesh *et al.*, 2018; Luz *et al.*, 2021; Mendonça-Gomes *et al.*, 2021; Kumari and Kumar, 2021). These drugs and their metabolites are included in emerging pollutants because they are not covered by regulations

and their concentration and effects on the environment are still poorly understood due to long exposure to residual levels (Corcoll *et al.*, 2014; Daughton, 2014), as they are designed to be biologically active, even at trace levels, and may exhibit unwanted effects on target and non-target organisms (Zhou *et al.*, 2016).

In this context, Brazilian legislation is not very restrictive for effluents contaminated with drugs and their limits for disposal in water bodies, without criteria with maximum values allowed for the concentration of these pollutants in water. The potability of drinking water for human consumption, stipulated by Consolidation Ordinance No. 5, of September 28, 2017 (Brasil, 2017), does not refer to the permitted limits for the presence of pharmaceuticals in supply water. Resolution 357/2005 related to the quality of water resources, defined by the Ministry of the Environment through the National Council for the Environment (CONAMA) and in CONAMA Resolution 430/2011 (CONAMA, 2011) responsible for establishing conditions and standards for the release of effluents for organic substances and inorganic substances, also do not address threshold standards for these pollutants.

There may be diverse consequences of this type of pollution on aquatic organisms ranging from small biochemical changes, damage at the cellular level, or even death, according to the mechanism of action and severity of the toxicological effect (Bernet *et al.*, 1999; Ramesh *et al.*, 2018; Mendonça-Gomes *et al.*, 2021). Indirectly, it can also increase the susceptibility of organisms to pathogens, promote the prevalence of diseases in the aquatic ecosystem and cause changes at the population level (Ellis *et al.*, 2011; Silvestre, 2020; Ali *et al.*, 2021).

Thus, considering that the presence and increase of chloroquine and hydroxychloroquine in aquatic environment can affect these animals' health, this article presents a theoretical approach based on a literature review discussing detection and removal strategies, estimates of Predicted Environmental Concentrations (PECs) and the ecotoxicological effects for aquatic biota attributed to drugs.

2. MATERIALS AND METHODS

A literature review was conducted following a semi-systematic methodology, where the search strategy may or may not be systematic, with qualitative analysis and evaluation, contributing to the state-of-the-art knowledge and related subjects in the literature (Snyder, 2019). The review process was carried out using the Web of Science® (www.webofknowledge.com) and Scopus® (https://www-scopus.ez31.periodicos.capes.gov.br/) databases. While for extracting the pharmacokinetic and physicochemical values of the drugs, the PUBCHEM® and DRUGBANK® databases were used (https://pubchem.ncbi.nlm.nih.gov/; https://www.drugbank.ca/). Our investigation included a combination of the following terms: "chloroquine" or "hydroxychloroquine" and "water", "sewage", "determination", "toxicology" "COVID-19". Eligibility criteria were applied to each publication, which consisted of the scope and availability of data without any date.

Then, studies were selected and grouped into key themes, as follows: (a) water contamination by aminoquinolines (detection and environmental concentrations); (b) estimates of predicted environmental concentrations during the pandemic; (c) removal methods and (d) ecotoxicity to aquatic organisms.

3. RESULTS AND DISCUSSION

3.1. Contamination of water by aminoquinolines and detection

Aminoquinolines and their metabolites can reach surface water bodies through different sources, such as inadequate disposal, effluents from hospitals and pharmaceutical industries, and mainly through human excretion (Araújo *et al.*, 2021). Having a high oral dose absorption, these drugs are metabolized by Cytochrome P450 and eliminated in patients' feces and urine

corresponding to 50% of the ingested dose in the original form or metabolites such as desethyl chloroquine (chloroquine N-dealkylated by CYP2C8 and CYP3A4) or desethyl hydroxychloroquine (hydroxychloroquine N-dealkylated by CYP3A4), and can be detected in biological fluids months after a single dose (Ducharme and Farinotti, 1996; DRUGBANK, 2022a; 2022b).

Depending on the hydrology of the system and the physicochemical characteristics of the drugs, their residues can accumulate in sediments, infiltrate into groundwater, or become persistent available in the surface water of lakes, rivers and reservoirs, used as drinking water and for agricultural irrigation (Quadra *et al.*, 2017). The aquatic bioavailability of these compounds can be explained by the molecular size, water solubility, n-octanol-water partition coefficient (Kow) which favors passage of drugs through membranes and bioaccumulation, ionization constant (pKa) favoring absorption at alkaline pH, non-volatile under normal temperature conditions and chemically stable, although this information is poorly standardized in the literature, values such as 0.0175 mg mL^{-1} to 100 mg mL^{-1} are cited for solubility of chloroquine compounds and 0.0261 mg mL^{-1} to 100 mg mL^{-1} for hydroxychloroquine compounds (Table 1).

Its environmental detection can be a problem due to low concentrations identifying it as non-existent when methods are not refined to identify them. Among the detection and quantitative determinations, methods for drugs and their metabolites are liquid chromatography, capillary electrophoresis, electroanalytical, spectrophotometric, and ELISA-based methods (Saka, 2020).

Chromatography was the method most used by the articles in the detection of CQ and HCQ due to the lower detection limit contemplating environmental concentrations in the range of ng L^{-1} to µg L^{-1} levels (Roberts and Bersuder, 2006; Tegegne *et al.*, 2021). The High-Performance Liquid Chromatography (HPLC) and Ultra High-Performance Liquid Chromatography (UPLC) techniques can be mentioned with the selection of detectors such as Ultraviolet, Fluorescence, Diode-Array and Mass Spectrometry which, when integrated, presented a high degree of sensitivity, selectivity and specificity for the compounds. In the papers, these methods were used primarily for the diagnosis of drugs in biological fluids (e.g., blood, plasma, and urine) (Tett *et al.*, 1985; Sanghi *et al.*, 1990; Chaulet *et al.*, 1994; Walker and Ademowo, 1996; Füzéry *et al.*, 2013; Singh *et al.*, 2015; Wang *et al.*, 2012; Harahap *et al.*, 2021), biomarkers (Ducharme and Farinotti, 1997), pharmaceutical samples (Dongre *et al.*, 2009) and in water (Roberts and Bersuder, 2006; Olaitan *et al.*, 2014; Nason *et al.*, 2021).

The capillary electrophoresis method was more used for quantification (ng mL^{-1}) in biological fluids (Müller and Blaschke, 2000; Oliveira and Bonato, 2007) while spectrophotometric methods were more used for pharmaceutical samples (µg mL^{-1}) (Reddy *et al.*, 2004; Nelson *et al.*, 2010). The Elisa method has been considered both for the determination and quantification (ng mL^{-1}) of drugs in biological systems (using antibodies) and also in pharmaceutical formulations (Khalil, *et al.*, 2011; Shenton *et al.*, 1988). These methods were more limited for drug molecule analysis and their metabolites in water.

Electrochemical methods are another promising alternative because they are modern, low cost, accurate, selective, fast and have a wide range of linear concentration (µM and nM) (Saka, 2020). Cork-graphite sensors (Araújo *et al.*, 2021; 2022) for hydroxychloroquine and glassy carbon modified with graphene oxide (Srivastava *et al.*, 2019), carbon pulp modified with nanowire $Cu(OH)_2$ (Mashhadizadeh *et al.*, 2009) for chloroquine were some examples applied in the voltammetry technique, which refers to the examination of the density potential curves of an electrochemical system, detecting concentrations of standard aqueous solutions of CQ and HCQ, which can be tools for monitoring of drug in effluents with higher concentration.

Table 1. Chemical formulas and predicted properties of compounds and their major metabolites.

Compounds and metabolites	Molecular Formula	Molecular Weight (g mol^{-1})	pKa	Kow	Solubility (mg mL^{-1})	Reference
Chloroquine	$C_{18}H_{26}ClN_3$	319.9	10.1	4.6	0.0175	DRUGBANK (2022a)
Chloroquine phosphate	$C_{18}H_{32}ClN_3O_8P_2$	515.9	10.3	3.9	0.0175 100	DRUGBANK (2022c); British Pharmacopoeia (2013)
Desethyl chloroquine	$C_{16}H_{22}ClN_3$	291.82	-	3.8	-	PUBCHEM (2022c)
Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	335.9	9.6	3.6	0.0261	DRUGBANK (2022b);
Hydroxychloroquine sulfate	$C_{18}H_{28}ClN_3O_5S$	434.0	9.7	2.8	0.0261 100	DRUGBANK (2022d); British Pharmacopoeia, (2013)
Desethyl hydroxychloroquine	$C_{16}H_{22}ClN_3O$	307.82	-	2.7	-	PUBCHEM (2022d)

3.2. Concentrations in the aquatic environment

Published studies on the concentrations of chloroquine and hydroxychloroquine in the environment are extremely limited but reveal the presence of aminoquinolines in surface and wastewater, having increased in recent years and especially during the pandemic. Chen *et al.* (2013) detected, through high performance liquid chromatography/mass spectrometry, the compounds in surface sediments near rivers in southeastern China. Although this study did not confirm the structural identities, each was reported in the sediments of at least one of the analyzed rivers at levels sufficient to provide signal-to-noise relationships.

Olaitan *et al.* (2014) detected residual concentrations of chloroquine in Nigeria through high performance liquid chromatography, which was 5.014 μg L^{-1}in groundwater and 0.11 μg L^{-1} in surface water. Also in Nigeria, studies were carried out by Hu *et al.* (2021) with data collected in 2017, chloroquine appeared among the pharmaceutical compounds identified with the highest relative abundance (1×10^5) in effluents, surface waters, wastewater and in tap water identified through high-resolution mass spectrometry. This may be related to being one of the countries with the highest incidence of malaria (WHO, 2020) and suggests that this compound was mainly from inefficient treatment processes in Wastewater Treatment Plants (WWTP).

Nason *et al.* (2021) monitored during the first wave of COVID, through liquid chromatography - high resolution mass spectrometry, elevated concentrations of hydroxychloroquine close to 50 μg L^{-1} in the primary sludge of a WWTP in the third week after implementing the United States Emergency Use Authorization, demonstrating its intense occurrence during the pandemic. That could be explained by 483,425 excess fills of hydroxychloroquine/chloroquine during the ten-week period in 2020 compared with 2019 (+848.4% increase) (Vaduganathan *et al.*, 2020).

In Europe, studies have reported a notable increase in hydroxychloroquine consumption in Athens, Greece, from 12 g day^{-1} to 57 g day^{-1} according to data published in the first months of the pandemic revealed by wastewater-based epidemiology (Galani *et al.*, 2021). In the same way, the region of Lombardy, Italy, reached levels of up to 1.7 μg L^{-1} (Cappelli *et al.*, 2022) while in Vitória-Gasteiz, Spain, reached 0.071 μg L^{-1} in wastewater (Domingo-Echaburu *et al.*, 2022).

These data demonstrate that some regions where the use of aminoquinolines was not frequent before the pandemic as an anti-inflammatory or antimalarial, had a rapid and significant growth during 2020, which given their chemical characteristics may be concentrated in water bodies. Similar to Nigeria, the chronic concentration of aminoquinolines in Brazilian waters may have increased dramatically during the pandemic since sales of hydroxychloroquine grew by 113%, from 963,000 in 2019 to 2 million units in 2020, according to the Federal Pharmacy Council (CFF, 2001) (Ruiz *et al.*, 2021), but no data were found to compare the concentration in water before and during the pandemic. In this context, the estimates of predicted environmental concentrations (PECs) come as a practical approach to estimate the level of drug concentration in an aquatic environment (Franquet-Griell *et al.*, 2015; Kumari and Kumar, 2021) when data on concentrations detected in water are unfeasible.

3.3. Estimates of Predicted Environmental Concentrations (PECs)

The aminoquinolines have a long half-life, the environmental emission is spread over several days, and, consequently, the PEC calculation depends on the use regime (dose, interval and duration of treatment) and removal rate in the wastewater treatment units to obtain a predicted concentration in the receiving water body (Tarazona *et al.*, 2021).

Thus, estimates of PECs during the pandemic were revised (Table 2) for the worst realistic scenario with the whole population of a metropolitan area of Spain, assuming that 25% of the excreted drug was retained in the WWTP (Tarazona *et al.*, 2021). There was an estimate assuming 100% of the population treated and considering an effective drug removal rate in the WWTP of 63% (Kuroda *et al.*, 2021). There was also an estimate with the elderly population (over 65 years old) in the United States affected by COVID-19, considering the removal rate at the WWTP as a standard value of 50% due to lack of data in the literature (Kumari and Kumar, 2021).

Table 2. Predicted Environmental Concentrations (PECs) during the COVID-19 pandemic in wastewater and environmental waters.

Drug	PEC Raw Wastewater (mg L^{-1})	PEC Secondary Effluent (mg L^{-1})	PEC Surface water (mg L^{-1})	Reference
Chloroquine	1.20	0.64	0.06	Tarazona *et al.* (2021)
	857×10^{-6}	32×10^{-6}	3.2×10^{-5}	Kuroda *et al.* (2021)
	-	-	3.78×10^{-6}	Kumari and Kumar (2021)
Hydroxychloroquine	1.50	1.12	0.12	Tarazona *et al.* (2021)
	833×10^{-6}	783×10^{-6}	78.3×10^{-5}	Kuroda *et al.* (2021)

Even though the consumption level of hydroxychloroquine observed in surface water by Nason *et al.* (2021), Galani *et al.* (2021) Cappelli *et al.* (2022) and Domingo-Echaburu *et al.* (2022) was increased during 2020, it remained lower than the PECS in raw wastewater. However, it is not yet known whether these PECs concentrations can be obtained considering

areas without sanitation coverage as a realistic worst-case, while the drug removal value after passing through the WWTP may vary depending on the system adopted by it.

Data from 2018 indicate that almost half of the Brazilian population does not have access to sewage collection, only 46% of collected sewage is treated (Farias *et al.*, 2020), and in many municipalities, it is common to see raw sewage discharges directly into water resources (Montagner and Jardim, 2011). Moreover, the conventional processes used in WWTPs were not designed to eliminate drug residues, which has already been corroborated by occurrence data obtained in Brazilian research (Sodré *et al.*, 2010; Reis *et al.*, 2019; Santos *et al.*, 2020) explained by both the higher consumption and the intense release of sewage into water bodies.

Furthermore, the metabolite desethyl chloroquine generated by the degradation of chloroquine can reach an environmental concentration of 13×10^{-6} mg L^{-1} (Kuroda *et al.*, 2021) and desethyl hydroxychloroquine, the main metabolite of hydroxychloroquine, does not appear in any studies. Both also do not have known aquatic toxicology, showing a gap regarding drugs.

3.4. Removal of aqueous matrices

As chloroquine and hydroxychloroquine have a very stable structure and occur at extremely low concentrations, their removal is challenging (Archer *et al.*, 2017). Thus, several promising proposals for the degradation of these drugs with concentrations similar to those in the environment were tested, mainly taking into account the pandemic. Treatment of different aqueous matrices (synthetic or real) containing CQ and HCQ has been carried out by adsorption, photolysis, photocatalysis and oxidation. Many of these studies pointed out that the molecule of drugs can be affected by pH, with the rate of degradation by the tested methodology and is directly proportional to the increase in pH.

Batch adsorption of CQ by combining babassu coconut-activated carbon and graphene oxide (GAC-GO) through the effect of ionic strength, simulating a real effluent, demonstrated that the synthesized adsorbent has potential application for the treatment of effluents (Januário *et al.*, 2022). The adsorption of HCQ on *Cystoseira barbata* activated by H_3PO_4, the Agardh biochar derived from algae biodiesel industry residues (Gümüş and Gümüş, 2021) and by Algerian kaolin (Bendjeffal *et al.*, 2021) proved to be stable, spontaneous sources and efficient.

Oxidation of CQ has been investigated by the reaction with Fe (VI) ferrate, it has been shown to be rapidly responsive especially in the basic pH range and with increasing temperature (Dong *et al.*, 2022). Electro-Fenton oxidation from electrolyte oxidation on boron-doped diamond (BDD) anode surface (Midassi *et al.*, 2020) and photo-Fenton process on micro-sized Fe-MOF sheet (Wang *et al.*, 2022) were efficient approaches to promote the generation of hydroxyl radicals from the catalytic decomposition of H_2O_2 by Fe^{3+} /Fe^{2+} in solution resulting in a high efficiency of degradation and CQ removal. Electrochemical oxidation also efficiently removed HCQ from the actual river water sample using BDD electrodes in studies carried out by Araújo *et al.* (2022), and Bensalah *et al.* (2020) with the potential to be an excellent alternative method to treat effluents contaminated with HCQ and its derivatives.

A peroxymonosulfate (PMS) activation system was also demonstrated using single cobalt atoms (SA Co-$NC_{(30)}$) as high-efficiency catalysts, which can efficiently degrade chloroquine phosphate through a nonradical electron transfer pathway (Peng *et al.*, 2022). The photocatalytic activity of zinc oxide catalysts supported natural zeolite clinoptilolite, and the synthesis heterogeneous structure of beta bismuth oxide by titanium oxide for HCQ degradation also promoted the degradation of the drug (Silva *et al.*, 2021; Kargar *et al.*, 2021). The photolysis of HCQ at high pH can be increased with the presence of humic acids, nitrate and iron (III) due to the formation of hydroxyl radicals and their attack on the HCQ molecule, but in the presence of chloride, sulfate and bromide the photodegradation is inhibited (Dabić *et al.*, 2019).

Biological systems were also analyzed in degradation. Examples were the use of melanin-encapsulated *Escherichia coli* for continuous removal of the pharmaceutical model chloroquine

in a membrane bioreactor-based process (Lindroos *et al.*, 2019) and microbial degradation by *Actinobacteria, Bacteroidetes, Chloroflexi,* and *Proteobacteria p,* along with functional genes related to pathways such as degradation and denitrification of phenylethylamine in salt water (Hu *et al.*, 2022).

Thus, the revised techniques promise to be more efficient to contain these micropollutants than the systems adopted by Waste Water Treatment Plants (WWTP), such as activated sludge and biological sewage purification, the most used processes in Brazil. The revised techniques are more cost-effective and promote total destruction (mineralization) or produce less toxic molecules, unlike methods such as activated carbon and ozonation (Margot *et al.*, 2013; Lindroos *et al.*, 2019).

3.5. Chloroquine ecotoxicity in aquatic organisms

Thus, the aquatic ecotoxicological information available to date on chloroquine is limited to a few studies on acute oral toxicity in fish, cladocerans, plants, algae and bacteria, and sublethal effects on fish and mussels (Zurita *et al.*, 2005; Moore *et al.*, 2007; Rendal *et al.*, 2011; Ramesh *et al.*, 2018; Davis *et al.*, 2020). While for hydroxychloroquine there are reports of ecotoxicological effects on nematodes, fish, and amphibians (Table 3). Chloroquine and hydroxychloroquine are persistent at maintaining their active properties until the desired effects are achieved (Mezzelani *et al.*, 2016). Thus, they can assume high concentrations in organs such as kidneys and liver, as well as having an impact on neurological symptoms (PIM, 1994; PUBCHEM, 2022b) as demonstrated by biomarker changes.

The bioassay review using biomarkers demonstrated how these can be considered early warning signs in the field of environmental risk assessment revealing the health status of an organism, population and ecosystem (Gavrilescu, 2015). This can help to reproduce and understand possible environmental scenarios related to the indiscriminate use of drugs in 2020. A reflection of that was the concentration observed in surface water by Nason *et al.* (2021), Cappelli *et al.* (2022) and Domingo-Echaburu *et al.* (2022), which promotes changes in biomarkers of oxidative stress, neurotoxicity (acetylcholinesterase and neuromasts), decreased levels of total proteins and death in vertebrates (MacPhee and Ruelle, 1969; Luz *et al.*, 2021; Mendonça-Gomes *et al.*, 2021).

Considering the revised effective concentrations, the sensitivity of the test systems decreased as follows for chloroquine molluscs > plants > cladocerans > algae > fish > bacteria. This relationship was similar to other drug sensitivity tests with the highest sensitivity for freshwater arthropods and lowest sensitivity for proteobacteria (Calleja *et al.*, 1994; Lilius *et al.*, 1994). However, conflicting results on toxicity in different fish species have been published, with mortality at 0.0063 mg L^{-1} CQ for salmon (MacPhee and Ruelle, 1969) and only behavioral changes in rainbow trout with 0.12 mg L^{-1} CQ in 24-h (Tojo *et al.*, 1993).

When compared to hydroxychloroquine, this was more toxic to fish at the same concentration as chloroquine in the morphological modification of lateral ciliate cells (Davis *et al.*, 2020). A Brazilian study with an environmentally relevant concentration of hydroxychloroquine and, especially, when combined with azithromycin (administered together in COVID-19 treatment), demonstrating that the combination of these drug classes may also lead to a greater expression of toxicity in fish and amphibians (Mendonça-Gomes *et al.*, 2021; Luz *et al.*, 2021). Studies with native species, such as the *Physalaemus cuvieri* (Brazil) is an example emphasize the importance of knowing the sensitivity of species with wide occurrence in the national territory and that may have suffered from the still unknown environmental exposures of the drugs that was used indiscriminately during the pandemic.

Table 3. Chloroquine and hydroxychloroquine concentrations in studies that had significant marker changes compared to drug-free controls.

Drug	Organism	Duration	Concentration	Toxic effect	Reference
Chloroquine	*Chlorella vulgaris*	48-h	27 mg L^{-1}	Growth inhibition	Zurita *et al.* (2005)
	Cyprinus carpio	96-h	31.32 mg mL^{-1}	Increased alanine and aspartate aminotransferase; decreased lactate dehydrogenase; histopathological changes; death	Ramesh *et al.* (2018)
	Danio rerio	24-h	31.9 mg L^{-1}	Cell loss lateral line ciliates	Davis *et al.* (2020)
	Daphnia. magna	48-h	4 - 30 mg L^{-1} (pH 7 - 9)	Immobilization	Rendal *et al.* (2011)
	Daphnia. magna	48-h	9 mg L^{-1}	Immobilization	Zurita *et al.* (2005)
	Mytilus edulis	120-h	2 mg L^{-1}	Decreased lysosomal function	Moore *et al.* (2007)
	Oncorhynchus mykiss	24-h	0.12 mg L^{-1}	Behavioral changes	Tojo *et al* (1993)
	Oncorhynchus kzsutch	24-h	0.0063 mg L^{-1}	Loss of balance and death	MacPhee and Ruelle (1969)
	Poeciliopsis lucida	48-h	43 mg L^{-1}	Decreased lysosomal function	Zurita *et al.* (2005)
	Salix viminalis	67-h	3 - 34 mg L^{-1} (pH 6 - 9)	Transpiration inhibition	Rendal *et al.* (2011)
	Vibrio fischeri	48-h	126 mg L^{-1}	Luminescence inhibition	Zurita *et al.* (2005)
Hydroxychloroquine	*Danio rerio*	72-h	0.0125 mg L^{-1}	Decreased levels of total proteins and neuromasts of the head; oxidative stress; increased acetylcholinesterase (AChE)	Mendonça-Gomes *et al.* (2021)
	Danio rerio	24-h	35.5 mg L^{-1}	Cell loss lateral line ciliates	Davis *et al.* (2020)
	Marine nematodes		3.162 mg L^{-1}	Decline in the diversity of abundance and richness of sensitive species and favoring of tolerant species	Ali *et al.* (2021)
	Physalaemus cuvieri	72-h	0.0125 mg L^{-1}	Oxidative stress; decreased acetylcholinesterase (AChE)	Luz *et al.* (2021)

Another important factor that increases the toxicity of chloroquine highlighted in the studies by Rendal *et al.* (2011) is the influence of pH in alkaline medium (pH 9) compared to acidic (pH 6) or neutral (pH 7) medium. Due to the pKa (10), pH can have a great influence on the absorption and expression of its toxicity in alkaline aquatic environments, which must be between 6.5 to 8.5 (USEPA, 1996), or 6 to 9 in Brazil, to protect aquatic life (CONAMA, 2005). According to Esteves (2011), the pH in Brazilian rivers is quite wide, tending to be slightly alkaline due to the presence of carbonates and bicarbonates, representing an environmental risk by the toxicity of chloroquine.

Sublethal effects were demonstrated after thirty-five days of exposure with changes in aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase enzymes that are usually present in the heart, liver, kidney, aminoquinoline accumulation sites (Ramesh *et al.*, 2018) in which there are effective markers to analyze chemical toxicity for their rapid response and for being involved in the metabolism of proteins and carbohydrates, in addition to serving as stress indicators (Abhijith *et al.*, 2016; Gora *et al.*, 2018). In the study by Ramesh *et al.* (2018), the increase in changes in gill, liver and kidney tissue of carp by chloroquine was correlated over time. The reduction in lysosomal function was also a biomarker responsive to acute exposure at higher concentrations and, mainly, to chronic exposure, directly affecting the health of the organism due to the characteristic lysosomotropic agent of chloroquine (Meshnick, 1990).

The most responsive biomarkers in acute exposure were changes in acetylcholinesterase (AChE) activity in the mediation of the neurotransmitter acetylcholine and the reduction in fish head neuromasts, impacting the neurotoxic effect together with other metabolic dysfunctions such as the reduction of total protein levels and oxidative stress after three days of exposure to hydroxychloroquine at concentrations from 0.0125 mg L^{-1} (Mendonça-Gomes *et al.*, 2021). Other metabolic dysfunctions were reduced total protein levels and oxidative stress seen in hydrogen peroxide (H_2O_2) production, reactive oxygen species (ROS), nitrite (NO_{2-}), thiobarbituric acid reactive substances (TBARs), superoxide dismutase (SOD) and catalase (CAT). Thus, hepatic Cytochrome P450 activity (CYP450), responsible for the biotransformation of aminoquinolines, is a crucial marker of susceptibility to be evaluated as it determines the abilities of antioxidants for the detoxification of organisms (Burkina *et al.*, 2015; Mendonça-Gomes *et al.*, 2021) and should be tested after exposure of the animals over time to understand under which conditions it becomes unresponsive, leaving the organisms susceptible to diseases.

Concerning the environmental assessment for water pollution monitoring, the Predicted No-Effect Concentration (PNEC) is estimated using the limit concentration in surface waters in which adverse health effects are not expected over time divided by a factor of assessment for intraspecific or interspecific extrapolation (Schwab *et al.*, 2005). For chloroquine, studies show that even at low residual concentrations it can result in toxic effects on biota health. Tarazona *et al.* (2021) estimated a PNEC value of 0.12 mg L^{-1} for aquatic organisms, considering data from the taxonomic groups of algae, cladocerans, mussels and fish, while Kuroda *et al.* (2021) estimated an even lower value of 3.7×10^{-4} mg L^{-1}. For hydroxychloroquine, the concentration was estimated to 7×10^{-5} mg L^{-1} from 8.5×10^{-2} mg L^{-1} (Cappelli *et al.*, 2022; Domingo-Echaburu *et al.*, 2022). This difference in the assessments can be explained by the variation in the input parameters used in the PNECs for risk estimates; however, they do not change the ecotoxicological risks (Kumari and Kumar, 2021).

Although there is no specific study on the xenobiotic incorporated in the trophic chain, it is interesting to note that the repercussion of toxicity extends from primary producers, consumers, and decomposers, affecting the entire aquatic ecosystem and eventually the animals that feed on it. Fish and other seafood sources can be easily contaminated by aminoquinolines due to their bioaccumulative potential, as can be seen by Ali *et al.* (2021) for the nematode

community, which may be a route to human exposure to residues, concomitant with the consumption of contaminated water (Kumari and Kumar, 2021). Other concern is water stress caused by aminoquinoline residues present in untreated wastewater or without adequate treatment to remove the drugs, which are commonly used by developing countries in irrigation for crop cultivation (Yasmeen *et al.*, 2014), despite being a practice that poses risks to health and the environment, as seen for *Vigna Radiata*, which can lead to the production of oxidative factors, impacting productivity (Al-Mentafji, 2021).

It is also highlighted that pharmaceutical pollution in water during the pandemic can generate resistance to a number of diseases (Horn *et al.*, 2020). In the case of chloroquine, some strains of *Plasmodium*, the etiological agent of malaria, already show chloroquine resistance in the treatment of the disease in which the drug has a proven therapeutic potential (Benelli and Mehlhorn, 2016) and its availability in water can further aggravate this situation. It also presents toxicity to predators of its *Anopheles stephensi* vector, in the aquatic phase of its life cycle, disfavoring biological control (Murugan *et al.*, 2016).

Considering that aquatic organisms are often exposed to contaminants in their natural environment, this can lead to changes in their physiology and homeostasis by a complex set of adaptive responses that involve biochemical, metabolic and tissue changes. The main scientific or technological contributions that can be made in question are the possibility of knowing better the response of these organisms by interacting with the emerging contaminant with a bioaccumulative tendency in the aquatic environment, aiming to establish proposals for conservation and animal protection considering safe levels regarding contamination environment and aquatic biota preservation, mainly in South America where its use has been increasing in recent years.

3.6. Perspectives

There are still gaps to be understood regarding acute ecotoxicity with lethal (LC_{50}) and effective (EC_{50}) concentrations for different taxa and species and, regarding sublethal ecotoxicity, pathological changes that can be visualized through biomarkers. The desethyl chloroquine and desethylhydroxychloroquine metabolites, together with the chloroquine diphosphate and hydroxychloroquine sulfate (best selling formulation) with a molar mass higher than original compounds, have little or unexplored ecotoxicity. It is often unclear in the article which formulation of chloroquine the authors used so that they do not yet support discussions comparing chloroquine compounds, although phosphate salt is categorized as more toxic due to the phosphoric acid groups in its molecule (PUBCHEM, 2022a). In addition, morphological and behavioral changes of the animals can also be observed during the experiment as they can be one of the first signs of change that can be identified in an environment, which demonstrated a pathological condition in the individuals (OECD, 2019; Ramesh *et al.*, 2018; Tojo, 1993).

The results can be extrapolated to the environment as vertebrates used in toxicological tests, such as some fish species already standardized for these studies, can have up to 70% homology with the human genome and including genes associated with human diseases (Howe *et al.*, 2013). Therefore, it is essential to understand how the characteristics, including morphology, physiology, behavior and life habits of an organism, mediate susceptibility to wide-ranging environmental change.

Despite limited data on toxicity to aquatic wildlife, Zurita *et al.* (2005) were able to classify chloroquine as "R52/53 Harmful to aquatic organisms and may cause long-term adverse effects in the aquatic environment". Thus, chloroquine currently belongs to the hazardous substances database (N° 3029), as it has toxicity to human and animal health proven in studies (PUBCHEM, 2022b). As alternatives, it is important for the use of effluent treatment technologies that are economical and with less risk of generating long-term repercussions (Pacheco *et al.*, 2021), such models should receive more attention and planning for

implementation considering the urgency of mitigating pharmaceutical residues in water, especially in epidemiological scenarios and without effluent treatment.

4. CONCLUSION

Chloroquine and hydroxychloroquine may be available in water bodies to aquatic biota and their concentration may have increased during the pandemic period due to extensive use and low removal in WWTPs. Once the aquatic biota is available, even at low residual concentrations, it can reach non-target organisms, generating an ecotoxicological risk that can have toxic effects such as morphological, physiological, behavioral and population changes leading to the death of individuals. Factors such as the more alkaline pH of the rivers and the association with other drugs such as indiscriminate use of azithromycin were attributed to the greater expression of drug toxicity.

More studies are needed to detect drugs and metabolites in water and refine quantification on an environmental scale, as well as to investigate biota hazards based on environmentally relevant concentrations, taking into account locations without access to wastewater treatment as worst-case scenarios. Ecotoxicity tests with native species and with high sensitivity to the pollutant can help to understand and extrapolate the toxic effects to the local aquatic ecosystem. Long-term toxicity effects, exploring effect biomarkers, exposure and susceptibility, morphological and behavioral changes, including drug derivatives, will provide important data for the discussion and these are the proposals raised by this study.

Thus, it is urgent to adopt efficient methods to contain pharmaceutical micropollutants in wastewater and surface water, as these will not only be available to aquatic biota, but to the human population, which may cause public health problems that are still uncertain.

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