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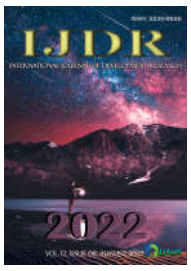

REVIEW ARTICLE **OPEN ACCESS**

INTENSIFIED USE OF CHLOROQUINE/HYDROXYCHLOROQUINE AND CONSEQUENCES ON ORAL HEALTH: A NARRATIVE AND SYSTEMATIC REVIEW

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ABSTRACT

In this article, the objective is to discuss, because of the pandemic resulting from the new Coronavirus (SARS-CoV-2) and the axis was bibliographic research carried out in the field of Dentistry, the intensification of the use of antimalarial drugs chloroquine and hydroxychloroquine and the consequences for the oral health of citizens. The data sources were scientific platforms, books, and texts selected according to their relevance to the theme, seeking to diversify the sources, carefully selected. Data indicate that the main occurrence with an impact on the oral health of these drugs is drug hyperpigmentation. It was also evident that there is a lack of up-to-date studies related to the subject in the field of dentistry, with dentists playing a central role in collaborating to maintain the overall health of patients. It means to say that as in-depth use of these drugs was identified, whose effects impact oral health, more studies must be carried out with this object of study in contemporary times, especially because of the intensification of the use, above all, of chloroquine during the experienced pandemic. It is expected that this study will contribute to those that will be carried out afterward, whether exploratory or in-depth.

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INTRODUCTION

With the pandemic caused by the new Coronavirus (SARS-CoV-2), called the COVID-19 pandemic, many challenges were imposed on various areas of knowledge, which was no different for Dentistry. Understanding that some factors contribute to the impairment of oral health, which increases the responsibility of the dental professional when performing a procedure on the patient and elaborating his treatment, it is important to understand how the pandemic affects the practice of these professionals. health field [1]. A broader understanding of the role of the dentist in contributing to the health of the individual as a whole is essential. It is in this perspective that this investigation develops. The Pró-Saúde (Program that intended to bring undergraduate training in the country closer to the needs of primary care, translated in Brazil by the family health strategy, was launched in 2005) [2], in the dynamics of the effort to reorganize and encourage to primary health care, understands that one of the important intersections between health and education concerns the adequacy of teaching, knowledge produced and services provided to the population-based on social needs, a situation that he recognized as being far from ideal and pointed out the need for the Higher Education Institutions incorporate the integral and terminal training of health professionals into their institutional mission, among which are the professions of medicine, nursing, and dentistry [2]. The health area as a whole, then, dedicated itself to seeking to understand how to deal with the new Coronavirus. The scant scientific knowledge about the behavior of this virus that initially appeared in Wuhan, China, the high speed of spread among the population, and the ability to cause very high mortality rates, especially in vulnerable populations, brought uncertainty about the best strategies to be employed [3]. Among the measures to contain its spread, the World Health Organization (WHO) recommended social distancing, the use of masks and constant hand washing, or the use of alcohol gel for hand disinfection. At the same time, research around an effective vaccine has intensified around the world [3]. When discussing the response to the contemporary pandemic, Werneck and Carvalho (2020) cite four phases [3]. We briefly discuss them, as they provide an overview of how the pandemic we are dealing with was generally addressed. The first phase is the containment phase, in which passengers arriving from abroad and people with whom they have had contact are actively screened, to prevent community transmission. Such a phase would have been crucial "so that the initial impact of the pandemic

was smaller in Taiwan, Singapore, and Hong Kong, even though they are close to China". The second phase, called mitigation by the authors, begins with the installation of sustained transmission of the infection in the country. The central strategy to reduce the transmission of the disease involves the isolation of identified positive cases (vertical isolation) and greater concern is focused on groups at greater risk of developing severe clinical conditions. Any activities that involve some kind of agglomeration need to be avoided by contaminated people, such as school activities, theaters, and cinemas, among others, it is what is called quarantine [3]. The suppression phase occurs to the extent that the previous ones were not effective, according to Werneck and Carvalho (2020) [3], either because of the insufficiency of diagnostic tests to identify infective individuals at the beginning of the epidemic or because of the reduction achieved in the transmission is insufficient to prevent the collapse in health care. In this phase that we are approaching, the measure of social distance becomes more radical, the entire population must adhere (horizontal isolation), that is, there is an extension of the quarantine, and the restriction of circulation becomes valid for everyone: the objective is to postpone the explosion of the number of cases, for a satisfactory time, "until the situation stabilizes in the field of health care, testing procedures can be expanded and, eventually, some new effective therapeutic or preventive tool (eg, vaccine) is available effective is available" [3]. The authors Werneck and Carvalho (2020) [3] recognize the controversies of this phase, due to the economic, social, and psychological repercussions on the population. Specifically in Brazil, we witness a lot of divergence between the federal, state, and municipal governments, being necessary, not infrequently, the judicialization to solve the cases. In a report, Gotti (2021) [4] shows the impasse, in the year 2020, requests came to the Judiciary so that schools, especially private schools, could reopen, and the movement was reversed at the end of that year and early 2021 when actions started to be filed to keep schools closed and teaching remotely. It is possible to cite the example of the decision of the 1st Court of the Public Treasury, which determined the suspension of classes in the public and private networks of Rio Grande do Sul, in Early Childhood Education and 1st and 2nd years of Elementary School, while the state was with the flag black (the phase considered most critical). Something similar happened in Pernambuco, at the 5th Court of the Public Treasury of Recife, where it was determined that the continuity of the suspension of face-to-face activities until the measures to guarantee the preservation of the health of education professionals were guaranteed, during the COVID-19 pandemic.

Finalizing the phases listed by Werneck and Carvalho (2020) [3] is the recovery phase, characterized by the consistency of signs of involution of the pandemic and the number of cases that becomes residual. The authors call attention to the importance of having an organization of society for the social and economic restructuring of the country. Having exposed the context, it is important to emphasize that the idea of early treatment for the new Coronavirus was used a lot, even though the WHO did not recognize its effectiveness, which, according to Melo *et al*. (2021) [5], a change in the pattern of drug consumption, which should be a point of special attention on the part of studies in the health area. Since what was called the "COVID-kit" was central during the period of the pandemic, supposedly aimed at early treatment, it is a combination "of medicines without conclusive scientific evidence for use for this purpose, which includes hydroxychloroquine or chloroquine, associated with azithromycin, ivermectin, and nitazoxanide, in addition to zinc supplements and vitamins C and D" [5]. Therefore, the present study aimed to investigate the possible impacts of the indiscriminate use of chloroquine/hydroxychloroquine on the oral health of individuals.

METHODS

Study Design: The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and meta-analysis, access available in: http://www.prisma-statement.org/).

Data Sources and Scope: The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases. The present study was carried out from January to April 2022.A qualitative approach was carried out, bibliographic research, developed from material already prepared, mainly scientific articles, which bring the approach up to date. According to Gil (2014, p.50) [6]: "The main advantage of bibliographic research lies in the fact that it allows the researcher to cover a much wider range of phenomena than the one he could research directly".

RESULTS AND DISCUSSION

Article Series and Eligibility: The total of 132 articles were found. Initially, the duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed. A total of 46 articles were fully evaluated and 21 were included in this study (Figure 1).

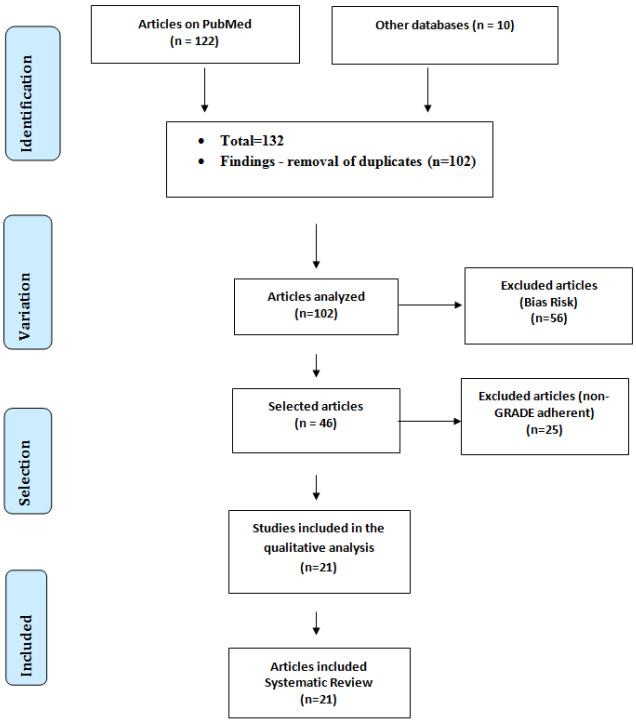

Figure 1. Flowchart showing the article selection process

Regarding the bibliographic research, Boccato (2006, p.266) [7] clarifies that:

> [...] the bibliographic research seeks to solve a problem (hypothesis) through published theoretical references, analyzing and discussing the various scientific contributions. This type of research will provide subsidies for the knowledge about what was researched, how and under what focus and/or perspectives the subject presented in the scientific literature was treated. Therefore, the researcher needs to carry out systematic planning of the research process, ranging from the thematic definition, through the logical construction of the work to the decision of its form of communication and dissemination.

Following these steps, this text is divided into four fundamental sections, the first being this introduction, which presents the context and general aspects of the study undertaken. Next, section 1 is presented, whose title is Controversy of chloroquine and hydroxychloroquine for early treatment, it brings an important discussion, considering what is known so far about the "main drugs that make up the 'early treatment' does have no scientific evidence of clinical efficacy or effectiveness, and its safety is still dubious to treat or prevent COVID-19" [5].

Section 2, Consequences for oral health: problematizing the effects of the use of chloroquine/hydroxychloroquine, is the one in which the possible effects on the oral health of the use of the drug in question are thought/indicated, according to the announced objective. The last section, in turn, is dedicated to the final considerations on the exposed theme and summarizes the results found.

The Controversy of Chloroquine and Hydroxychloroquine for Early Treatment: The sale of drugs for the supposed early treatment to avoid contamination by the new coronavirus exploded, with azithromycin, with a 30.8% increase in sales during the pandemic period. Adverse Drug Reactions (ADRs), from 2009 to 2018, were reported in 19 suspected cases associated with ivermectin in 10 years, according to Melo *et al*. (2021) [5], and in just nine months of 2020, in the current VigiMed system, 25 ADRs related to the drug have already been reported, with people who used it having nausea, diarrhea, abdominal pain, drowsiness, dizziness, and rashes. This indicates the research problem posed here. Barbirate et. al. (2020) state that clinical studies have tested possible drugs and therapeutic protocols to treat the disease, but the authors acknowledge that the results are controversial due to methodological limitations, and non-comparability between studies and a low or limited level of scientific evidence. Among the drugs tested are the 4-aminoquinoline antimalarials, chloroquine, and its derivative hydroxychloroquine. Hydroxychloroquine is known for its use against inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis and in the fight against malaria, especially in tropical countries. Germano, Mendonça, and Murinello (2005) clarify that: "Malaria is a serious public health problem with important repercussions on mortality rates in countries where it is endemic" and emphasize that among the most used drugs are chloroquine, mefloquine, the chloroquine/proguanil association, due to its pharmacokinetic characteristics, which allow for easy-to-adhere dosage regimens. Barbirate et. al. (2020) state that, in the states of the Amazon, for example, chloroquine and hydroxychloroquine have been widely used for years in the treatment of malaria (mainly in rural areas and in traditional populations such as riverside dwellers), with no reports of complications. serious medical conditions and the epidemiological impact of its use in these regions.

According to Melo *et al*. (2021, p.02), "hydroxychloroquine and chloroquine also had their revenues increased from R$55 million in 2019 to R$91.6 million in 2020". It is not possible to disregard that: "As a result of the increase in sales of these drugs, which can be considered a proxy for consumption, the anomalies derived from them, such as self-medication, bacterial resistance, and adverse reactions, also grow". Because of new analyzes carried out with data from notifications of suspected ADRs in patients contaminated by the new Coronavirus, updated until December 2020, it was identified that, as of September 2020, there was an important reduction in the registration of hydroxychloroquine and chloroquine drugs in the database in patients hospitalized for COVID-19, either as suspected ADRs or concomitant use. At the same time, research has shown an increase in retail sales of these drugs over the same period. The hypothesis of Melo *et al*. (2021) is that there has been an intensification of the use of these drugs in the outpatient scope, in which users are rarely monitored for the identification of cardiac alterations, which are often associated with the use of these drugs. Barbirate et. al. (2020, p. 62996), when investigating the effectiveness of the use of chloroquine (CQ)/hydroxychloroquine (HCQ) in the treatment of infections by SARS-CoV-2, state that: "Based on current scientific evidence, we conclude that although CQ/HCQ has low cost and easy access, and studies have shown benefits of these drugs in the treatment of COVID-19, it is not possible to say about their effectiveness".

Consequences for Oral Health: Problematizing The Effects of Chloroquine/Hydroxychloroquine Use: In this section, we seek to analyze the use of chloroquine/hydroxychloroquine drugs from the point of view of oral health promotion, understood as a result of actions that understand health as a resource for quality life, guided by the social and environmental conditions of life in the community, in addition to being built on a positive relationship between the human mouth and the biological body and the social body, a meaning indicated by Kusma, Moysés and Moysés (2011). Menezes, Sanches, and Checker (2020) state that the use of chloroquine and hydroxychloroquine follows a protocol that involves periodic ophthalmological evaluation, as well as the evaluation of liver enzyme levels, aiming at early detection of signs of liver toxicity, as "if pathology is detected in the initial phase,maybe reversible with discontinuation of the drug.Specifically, hydroxychloroquine, the same authors (ibid.) indicate that there is concern regarding cardiotoxicity in case of prolonged usein patients with chronic medical conditions such asrenal, hepatic or immunosuppressed, and there is also a risk of hemolysis or bone marrow suppression [11].

In their work, Menezes, Sanches, and Checker (2020) present results of analysis of research on these drugs and indicate, as an adverse effect of hydroxychloroquine, the development of torsade arrhythmia, development of myocarditis, rhabdomyolysis and segment prolongation QT (no arrhythmia specification). Considering the effects of the use of these drugs on health, the objective was to investigate whether there are and what would be the impacts people's oral health. It is essential to recognize the importance of dentistry within the population's health practices. In this sense, inter and transdisciplinarity are essential and it is in this perspective that we seek to investigate the effects of the use of chloroquine/ hydroxychloroquine on the oral health of the population. Jesus (2019, p.63) considers that the singularities of dentistry regarding "its development, singularities that, when reviewed through a retrospective in History, are very valuable instruments for understanding the current role that it exerts within modern society. In the research carried out by Amaral *et al*. (2014), in the field of dentistry, looking at the dental surgeon, it is stated that the chloroquine used by 41% of the patients surveyed, for the treatment of cutaneous manifestations, "can cause maculopathy by impregnation of the drug. in the retina and, if not recognized in time, can be responsible for debilitating changes in vision, such as abnormal color vision and visual blurring." In a study that analyzes the adverse effects of topical and systemic drugs on the oral mucosa, Loureiro *et al*. (2004) identify drugs that have the potential to cause adverse reactions in the oral mucosa. The authors warn that patients who develop intraoral symptoms due to drug therapy should seek health care professionals, so it is "evident the need for this professional to recognize them, to know the drugs commonly involved and to seek to establish a potential relationship between drugs and the oral adverse effects", through a well-performed and directed anamnesis. Among the drugs mentioned in the study are drugs used as antimalarials, such as chloroquine, which can promote the appearance of macular lesions with well-delineated edges on the oral mucosa.

In the study by Kleinegger, Hammond, and Finkelstein (2000) [15] a case of hyperpigmentation of the oral mucosa resulting from therapy with antimalarials was already indicated. The long-term therapy with quinacrine to which the patient was submitted caused him to exhibit diffuse blue-gray pigmentation of the nail beds and the skin of the nasal ala, and the microscopic examination of the involved mucosa showed macrophages, containing melanin and ferric iron, scattered in the connective tissue adjacent to the epithelium. Consolaro *et al*. (2011) [16] address oral hyperpigmentation induced by antimalarial drugs. It consists of a change in the normal color of the mucosal region. The authors describe that drugs that induce abnormal pigmentation of the oral mucosa are antimalarial agents, such as chloroquine and hydroxychloroquine. In addition to being antimalarial, these drugs have immunosuppressive and anti-inflammatory activities, which increases their spectrum of indications. The authors recommend that dentists should be familiarized with diagnosing macules in the oral mucosa, indicating the patient for a detailed systemic evaluation and definitive diagnosis of the disease. "Patients, and many professionals, often do not relate hyperpigmentation as a side effect of medication" [16]. The first report of hyperpigmentation in the oral mucosa (on the palate) due to the use of antimalarial drugs, according to Consolaro *et al*. (2011)

[16], was done by Lippard and Kauer, in 1945. Since then, other similar cases have been reported "and, in most cases, only in the hard palate, with a demarcation line with the soft palate, without a plausible explanation for these limits. Involvement of the gingiva and labial and buccal mucosa was eventually presented". Silveira *et al*. (2013) reiterate that antimalarial agents are associated with pigmentation of the skin, mucous membranes, and retina so among the most frequently involved are chloroquine and hydroxychloroquine. As a wide variety of lesions and conditions can result in abnormal mucosal pigmentation, in this regard, a systemic assessment is required, including complete and accurate patient history, as already indicated above in this text. Among the clinical characteristics that most help in the diagnosis of pigmented lesions are, according to Silveira *et al*. (2013), distribution and color, with a diffuse or multifocal distribution of pigmentation suggesting a systemic cause or drug toxicity.

In one of the clinical cases reported in their text, Silveira *et al*. (2013) [17] describe the case of a female patient, forty years old, who attended the Stomatology Service on the recommendation of the dentist, who noticed the presence of a change in the color of the palate mucosa. During the anamnesis, the patient reported being treated with chloroquine for about 12 months (for treatment of discoid lupus erythematosus). The dentist was a key figure, as the patient herself had not been aware of the change in the mucosa and had no symptoms. According to the authors, "due to the clinical characteristics of the stain, the reports in the literature and the history of the use of medication with immunosuppressive activity, it was not necessary to perform a biopsy to reach a conclusive diagnosis". When studying systemic lupus erythematosus therapy, which is based on the administration of corticosteroids and immunosuppressants to attenuate the immune system response, control symptoms, and prevent future complications, Santana (2016) states that antimalarials, especially hydroxychloroquine sulfate, are indicated to reduce disease activity and try to save the use of steroids, but the author warns of the need to monitor the side effects of prolonged treatment. With the intensification of the use of this drug during the pandemic caused by the Coronavirus, it is understood that the investigation of the effects on oral health must be detailed. Kusma, Moysés, and Moysés (2011) note an effort, over the last few years, to promote greater integration of oral health into health services in general, which allows for the synergy of knowledge and practices that promote surveillance of health, "action on social determinants of the health-disease process, prevention of risks and diseases, and the consequent incorporation of practices based on evidence of effectiveness".

In a recent study published this year, Holanda *et al*. (2021) aimed to survey case reports of oral pigmentation related to the chronic use of chloroquine and hydroxychloroquine, drugs used for a long time, but which the authors recognize are currently the targets of many studies due to the survey of the possibility, not scientifically proven, as previously mentioned in this text, to be effective against the new Coronavirus, either for prevention or treatment. These same authors also emphasize this in their study, stating that "at present, there is no scientific basis for the use of antimalarials in cases of COVID-19". Also, Holanda *et al*. (2021) [19] explain that, among the pathologies and gingival diseases not induced by the biofilm, pathological changes limited to the tissues of the periodontium, it is possible to find gingival pigmentation, which can occur due to drugs. Thus: Drug therapy-induced hyperpigmentation can be caused by increased melanin production with or without an increase in melanocytes, dermal deposition of the drug or its metabolites, production of pigments under the influence of the drug, or the destruction of red blood cells [19]. It is important to think about these aspects, considering that oral health is not detached from the general health of a person and that dentists play an essential role in maintaining this harmony, as they can identify and refer to appropriate treatments, in case they run away from competence to treat a certain identified pathology. Even the formation of a healthy human being, with awareness of his body and its functionalities, necessarily involves the adoption of oral health care. Because of the results obtained so far, one might think that hyperpigmentation is just an aesthetic issue, but it should not be reduced to that, because its appearance can resemble malignant lesions, for example, melanomas. When surveying scientific articles, using the descriptors hyperpigmentation, chloroquine, and hydroxychloroquine, Holanda *et al*. (2021) explain that the dental team must be very attentive to the signs and symptoms in patients who use chloroquine, so that an early diagnosis is carried out, as well as the necessary referrals to other specialties, since it is known that pigmentation by the use of this drug may be an indicator of ocular involvement, which may lead to the development of retinopathies, sometimes irreversible and, in more severe cases, may lead to total loss of vision. As for the predominant profile of patients who presented melanin pigmentation due to the effects of drug use, women are among the most sensitive, according to Holanda *et al*. (2021), probably due to the interaction with sex hormones. The results obtained also indicate that: the hard palate was the region of the oral mucosa most affected by pigmentation caused by the use of antimalarials, with patients, in most cases, having a blue-grey color; the use of chloroquine was prevalent to that of hydroxychloroquine, that is, in most cases raised in the study. Therefore, the impacts that the COVID-19 pandemic caused on people's lives were varied, both social and economic (which, in many cases, involved the risk of not being able to maintain subsistence), as well as there is no dimension of which ones. will still emerge, for example, as to the psychic results of social isolation. Amid the immense desire to find something that could contain the spread and the number of deaths, which, in Brazil, exceeded the number of half a million people, the hypothesis arose (fed by public managers) that chloroquine/hydroxychloroquine would affect this sense. It should be emphasized that this is a major concern shared by several countries, but the global urgency has always been for a safe and proven antiviral therapy. As seen in the course of this work, it is not a proven hypothesis, it is even vehemently criticized by most health professionals, due to the lack of studies that indicate its effectiveness outside of what was thought: treatment of malaria and hepatic amebiasis, in addition to indicated for the treatment of rheumatoid arthritis, systemic lupus erythematosus and discoid lupus, sarcoidosis and photosensitivity diseases such as porphyria cutanea and severe polymorphic light-triggered eruptions. It is noted, then, that the hypothesis is born from the idea that its action against inflammation would be an alternative to treat people and contain the pandemic outbreak declared on March 11, 2020, by the WHO. Before that, in February 2020, the Brazilian Ministry of Health declared a Public Health Emergency of National Importance due to human infection with SARS-CoV-2.

The fact is that such a hypothesis and recommendation, even if not proven and without indication by the World Health Organization, caused the consumption of such drugs to skyrocket. Considering specifically Dentistry, the object of study of this work arises from the observation of the use of chloroquine/hydroxychloroquine as possible drugs to be used in the early treatment against contamination by the new Coronavirus (SARS-CoV-2) and/or to deal with its effects. From this arose the scientific question: what are the consequences for people's oral health? From this, bibliographic research was designed to investigate the intensification of the use of the antimalarial drugs chloroquine and hydroxychloroquine, in the field of Dentistry. Besides, Narvai (1994) presented the following dentistry: sanitary, preventive, social, simplified, integral, community, also, collective oral health, analyzing them one by one considering the contexts in which they emerged and exploring their connections with more general proposals for the health sector and with different projects for society. Social and preventive dentistry, for example, had its most prominent period in the period of the military dictatorship (1968-1978), entering into decline in the 1980s. The author is brought in to emphasize the idea of a dental practice that contributes to the general health of individuals, which is not confined to the mouth but is part of the subject's organic whole [21].

CONCLUSION

The data collected in this research indicate that the main occurrence with an impact on the oral health of antimalarials (chloroquine and

hydroxychloroquine) are dark spots in the mouth, called drug hyperpigmentation, which is a change in the normal color of the mucosal region, as indicated by the throughout this text. Therefore, clinical monitoring to identify and control possible changes is essential. Even for the reason that hyperpigmentation can indicate more serious issues associated with the individual's health. However, an important warning that this study leaves is the identification of the low number of scientific studies related to Dentistry at a time when the aforementioned drugs are being stimulated and their use has increased exponentially, despite their efficiency to prevent or treat the new Coronavirus. proven and not recommended by the World Health Organization. We emphasize the need for further studies to be carried out to map the impact of chloroquine and hydroxychloroquine on the oral health of individuals in this period in which their use has been disseminated, which can even establish a total score (extension, intensity, and pigmentation), and considering the role that the dental professional assumes in the proper anamnesis.

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Ethics Approval: Not applicable.

Informed Consent: Not applicable**.**

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Conflict of Interest: The authors declare no conflict of interest.

Similarity Check: *It was applied by Ithenticate*[@].

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