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Wide Applications of Chloroquine Other Than Antimalarial

Baraa G. Alani[1], Ameer H. Alwash[1], Ismail T. Ibrahim[1,2]

[1]Faculty of Pharmacy, AL-Bayan University, Iraq, Baghdad
[2]Hot Lab Center, Atomic Energy Authority, Cairo, Egypt
Email: ismailtaha_73@yahoo.com

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Abstract

Chloroquine (CQ) was and still considered as the most common agent in the treatment and prophylaxis of malaria, it also possesses many different pharmacological and biological activities that make it able to be used as a therapy or adjuvant therapy for many types of diseases. CQ exhibits anticancer activity alone or as adjuvants with other agents against many kinds of tumors. Its activities also were approved as an anti-inflammatory agent in rheumatoid and other autoimmune diseases like systemic lupus and rheumatic arthritis. Its' important role in the improvement of many metabolic disorders like hypertension, hyperglycemia, and lipid profile disturbances was also established. CQ can act against different microbial infections such as many types of viruses, bacteria and fungus by different mechanisms of action. Furthermore, its dermatological role in the treatment of many skin diseases was demonstrated. Recently, CQ showed a very responsive role in curing and prevention of the covoid-19 virus. This review summarizes intensively the multiple therapeutic applications of CQ and discusses the possible mechanisms of action for these applications.

Keywords

Chloroquine, Antimalarial, Anticancer, Autophagy

1. Introduction

Chloroquine (CQ) is 4-aminoquinoline that has been used for more than 70 years as an antimalarial agent. Its development was started from natural product as its distance precursor quinine was isolated from crude extract of cinchona bark that was been used for reducing fever and malaria for long time [1]. CQ had been synthetized since 1934 by German Farbnindustrie Bayer Laboratories [**Figure 1** and **Figure 2**] [2]. CQ was considered the drug of choice for malarial

infection for several years till its antimalarial role was reduced by emergence of CQ resistant strains of malarial parasite [2]. CQ is often used alone or together with other compounds to treat many biological disorders other than malaria, such as cancer, inflammatory conditions, hypertensive crises in some cases, high level of blood sugar, dyslipidemia, and different microbial diseases [3] [4]. For a long time it was used in the clinic to treat autoimmune diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) by inhibition of the immune system and by its anti-inflammatory properties [5] [6]. Its potent cytotoxic effects against different types of cancer such as colorectal, lung, breast, hepatocellular and human cervical cancer were observed [7] [8]. The weak basicity of CQ molecule with pKas of 8.4 and 10.2 [9] [10] makes it able to accumulate in acidic organelles such as lysosomes, endosomes, Golgi apparatus and interfere with the activity and hydrolysis of the lysosomal enzymes by increasing the pH lumens of these organelles, therefore makes inhibition to the autophagy process which is involved in many biological disorders [11]. Short term administration of CQ may not induce toxicity but longer exposure has been associated with some dangerous side including irreversible retinal toxicity, bone marrow suppression, cardiomyopathy and hypoglycemia [12] [13]. Hydroxychloroquine sulfate (HCQ), is a famous derivative of CQ, was first synthesized in 1946 by addition a (OH) functional group to CQ pharmacophore that make it less toxic by (~40%) than original CQ in animals trials (**Figure 2**) [14]. HCQ is still widely available to treat autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematous. It is important to say that Chloroquine and Hydroxychloroquine share similar mechanisms of acting and chemical structures and both of them are weak bases and immune-modulators [15]. Although there are many reviews about Chloroquine and its therapeutic effects on different diseases and disorders, the majority of them focus on a limited therapeutic strategy with its mechanisms of action by which can improve or treat specific disorders such as; anticancer or antimicrobial etc. This study was conducted to cover in more details as possible as diseases and disorders that CQ and HCQ could be used to treat them as well as the mechanisms by which they can manage them. It also extended to show the most observed side effects of CQ.

2. Therapeutic Indications of CQ and HCQ

2.1. Anticancer

Cancer means lose the cellular ability to control and regulate their cycle and gain the ability of unlimited cell proliferation, division that finally produce a mass of cells called tumor [16]. Cancers have many different mechanisms and molecules to enhance their growth and metastasis by enhancing malignant cells to cope with the bad micro-environmental conditions like hypoxia and low nutrients [17].

Anticancer activity of CQ and HCQ was well established and demonstrated *in-vivo* on colon cancer, lung and breast cancer or *in-vitro* on cancer cell lines.

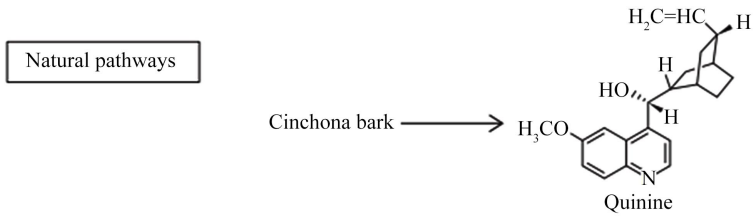

Figure 1. Quinine structure (2).

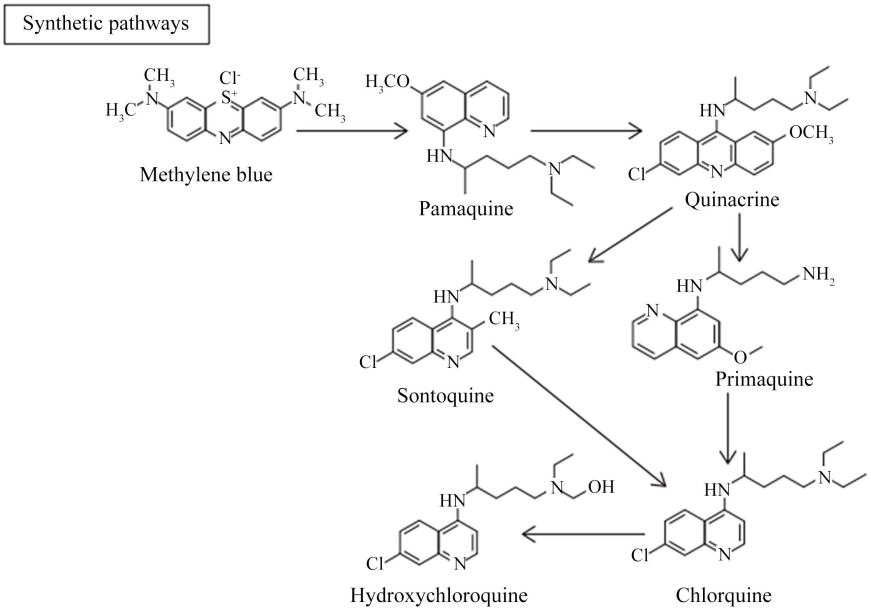

Figure 2. Synthetic pathways of CQ and HCQ (2).

Also, they have excellent potential as cancer-specific chemosensitizer for combination therapy as an adjuvant with other anticancer agents [18].

2.1.1. Mechanism of Anticancer Effect of CQ, HCQ

There are multiple hypotheses proposed on how CQ, HCQ exert their anticancer activity when given as mono or adjuvant therapy. For their anticancer activity, CQ and HCQ have multiple mechanisms of action that might complement each.

1) Inhibition of Autophagy

The main mechanism to which, the anticancer effect of CQ was attributed is inhibition of autophagy (self-eating) [19]. Autophagy is a biological process by which cytoplasmic organelles are eliminated by lysosomes that contain lysosomal degradation enzymes. Up to date, there are three types of autophagy are known micro-autophagy, macro-autophagy, and chaperone-mediated autophagy. They are different by their initiation, mechanisms involved in, and destructive mode during delivery to the lysosome [17] [18]. Autophagy mostly referred to macro-autophagy, is survival mechanisms when cells undergo stress and unsuitable conditions like increasing temperature, low nutrients level, or diminishing amount of oxygen needed. That means autophagy plays important role in biological processes by keeping the hemostasis of the cells [19] [20]. In anoth-

er side autophagy also having a harmful role that it may contribute to several human disorders like cancer, neurodegenerative diseases like Alzheimer and Parkinson [21]. Autophagy may be implicated in both innate and adaptive immune system defense. It also presents during the total different inflammatory steps and it has been eliminated many cellular invaders like viruses, bacteria, and parasites.

There are two opposite hypotheses on the role of autophagy in cancer. The first suggests that autophagy may promote cancer cell survival [22] [23] [24], but the other suggests the opposite that it may participate in the inhibition of malignancy and limit cancer cells ability to accumulate genotoxic reactive oxygen species [25]. The last one explains the main mechanism of the anticancer effect of CQ and HCQ.

First hypothesis, indicates that the suppression of autophagy can enhance oncogenesis through alteration of the metabolic pathways and produce oxidative stress, that totally lead to helpless mitochondrial turnover [26] [27], inducing genetic instability (which is a consequence of oxidative stress) [28] [29] [30], enhancing Oncogenes impairment to induce senescence, (a process that blocks the malignant cells proliferation permanently while allows their turnover by immune cells) [31] [32] [33]. For this hypothesis, the treatment approach that able to enhance the autophagy process, will be a promising strategy for cancer progression inhibition.

On other hand, the second hypothesis states that autophagy able to facilitate tumor progression and neoplasm establishment [34] by enhancing their coping with the micro-environment hard conditions through providing a source of energy and nutrients to abnormal cell [35] preserving both functions of mitochondria which are controlling the quality of its network and providing metabolic substrate from mitochondria metabolism [36] and finally decreasing the accumulation of potentially cytotoxic entities like reactive oxygen species [37] [38] [39] [40]. According to this hypothesis; the treatment strategy that works to make suppression to autophagy is effective as anticancer therapy or adjuvant therapy [41] [42].

To set in between some types of cancer may be enhanced with autophagy and other could be inhibited with it [43].

CQ, HCQ as weak bases having good safety profile [43], and become protonated in acidic compartments like lysosome and late endosome. It can fuse with these acidic compartments resulting in blocking the flux of stimulating autophagy [44] that will lead to inhibition of lysosomal activity of the autolysosome, hence stopping the degradation. Therefore there is no energy supplying through autophagy pathway because autophagy can promote cancer according to 2nd hypothesis, cancer progression can be stopped by stopping it.

2) Other mechanisms:

Chloroquine showed additional mechanisms for cancer treatment other than autophagy inhibition.

CQ may also enhance the blood vessels normalization which results to reduce

the tumor hypoxia through improving the functional and structural features of tumor blood vessels [45] [46] since the appearance of disorganized and dysfunctional blood vessels is the most important feature of many cancers, since they become permeable and enhance the facilities of tumor invasion and progression. In addition CQ can improve these vessels by decreasing the density and tortuosity of tumor vessels that result in improvements in endothelial cell arrangement and formation of tight junction, it also contributes to reducing the leakiness of tumor vessels and elevates their perfusion. It is important to say that the normalization of tumor vessels also enhance the efficacy and delivery of other chemotherapeutic agents [47]. Therefore this action reduces the survival capacity of cancer cells in the blood stream and becomes unable to be metastasized. Because of conformational changes that the autophagy provides blockage of cancer cells will reduce the metastatic propagation rather than prevention.

CQ was shown to suppress pancreatic ductal adenocarcinoma (PADC) and cancer stem cells (CSCs) which are known to be resistant to many medicines and promote tumor progression and metastasis [48]. In animal of PADC, Chloroquine showed its ability to target CSCs by inhibition of signaling pathways that driven by chemokine, leading to suppression of signal transducer and activator of transcription 3 (STAT3) and extracellular signal kinase (ERK), that have a very critical role in metastatic spread [49]. It is able to block epithelial mesenchymal transition in CSCs. Moreover, it can target CSCs in triple-negative breast cancer via down-regulation of multiple signaling pathways like STAT3 that produce decreasing in CSCs [50].

a) Interference with the p53 pathway

The tumor suppressor protein p53 plays an essential role in maintaining an error-free genome and inducing cell death in case the damage is irretrievable. Therefore, it is a key protein in the prevention of tumor development [51] [52]. Both *in vitro* and *in vivo* research has indicated that CQ can stabilize the p53 protein and activate the p53-dependent transcription of pro-apoptotic genes. So CQ intercalates in DNA, which leads to structural changes and thus induction of p53 [53] [54] [55] [56] [57].

2.1.2. CQ as Adjuvant

Adjuvant CQ is a promising candidate for combination with a variety of cytotoxic agents for the prevention of CSCs driven tumor progression [58]. CQ as adjuvant uses is also due to its ability to sensitize cancer cells to other therapeutic agents by alteration of non-CSC-specific signaling pathways. Treatment with CQ has been shown to improve Cisplatin therapeutic efficacy to DNA damaging and mammalian target rapamycin (mTOR) inhibitor in breast cancer cells [59]. This chemo-sensitization being independent of autophagy inhibition mechanism, as exposure to the autophagy inhibitor Bafilmycin failed to decrease cell viability. In addition, blocking of genes that enhance autophagy like autophagy related protein 12 (Atg 12) and Beclin-1, cannot resemble CQ effects [60]. The most effective mechanism by which CQ can induce drug sensitization include

DNA intercalation and promote the activation of ataxia telangiectasia mutated (ATM) and P53 [61].

CQ can also penetrate the malignant cells and enhance the radiation response of tumor cells culture. It was also found that CQ can effectively sensitize multi-drug resistance tumor cells to certain anticancer agent [62].

Finally, CQ as a drug act by anti-autophagy pathway or other mechanisms it becomes a very useful therapy to treat many types of cancer like pancreatic adenocarcinoma, prostate cancer, breast cancer, ovarian cancer and renal cell carcinoma [63].

2.2. Anti-Inflammatory

CQ has been used as an anti-inflammatory drug for systemic lupus erythematous (SLE) and rheumatoid arthritis (RA) by modulating the immune system [64] [65]. SLE is an autoimmune disorder that may affect a number of organs and tissues of the body associated with skin lesions [66].

Many studies demonstrated that the administration of CQ can inhibit angiogenesis and a significant decrease of dermal blood vessels [67]. Under *in vitro* conditions, it can induce apoptosis of human endothelial cells and decrease cells proliferation and reducing the levels of angiogenesis [68]. It is able to improve and decrease the sign and symptoms of SEL in joints and epidermal lesions [69]. CQ seems to be an anti-angiogenic agent by decreased expression of VEGF and CD34+ blood vessel number [67]. RA is a chronically progression systemic autoimmune disease associated with extra-articular manifestations like malaise and fatigue [70]. RA had been reported to affect near to 1% of adults population of affected regions [71] [72]. This disease varies from simple self-limited to sever and joint destruction with intense physical disability and multiple morbidities [73]. Many immune modulators like pro-inflammatory cytokines play a critical role in RA pathophysiology [74]. Native T cells differentiate into Th cells which result in potent cytokine IL-17 production that promotes synovitis. B cells are also involved in pathogenic process by antigen presentation to self-antibodies and cytokine productions [75] [76]. These manifestations of RA are both locally and systemically and describe an inflammatory condition [77].

Mechanism of Anti-Inflammatory Effect

Different modes of action are explained the anti-inflammatory effects of Chloroquine, mostly are approved by *in-vitro* studies. The relations between the therapeutic efficacy, mode of actions and safety were observed *in-vivo* [78]. The most essential mode of action of this compound is the ability to interference with the autophagy and lysosomal activity by inhibition their function, it can make destabilize lysosomal membrane and stimulate releasing of its enzymes inside the cells [79]. This lysosomal activity inhibition might inhibit lymphocytes function that results in immunomodulatory and anti-inflammatory effects (exactly anti-rheumatic effects) [80].

Inhibition signaling pathways are another mode of action of CQ which can

produce own anti-inflammatory action. This mechanism is done by the interference of this compound with the activity of cyclic guanosine monophosphate adenosine monophosphate (cyclic G-AMP) synthase [81], in which when it being stimulated, it able to enhancing IFN genes pathway which is the major source of type I IFN response. IFN-I is the gene that is strongly implicated in pathogenesis of many inflammatory and autoimmune disorders like RA [82] [83]. So G-AMP inhibitor like Chloroquine is suitable therapy for this inflammatory rheumatic pathway [84]. The other anti-rheumatic mode of action of Chloroquine is summarized by reducing the inflammatory cytokines by various cells type. In *in-vitro* study; this drug able to inhibit the production of IL-1, IL-6 and TNF in mononuclear cells [85].

Also anti-inflammatory effect of CQ may be achieved through inhibition of arachidonate cyclooxygenase and inhibition of PG synthesis. The anti-inflammatory effectiveness of CQ could be also partly explained by its PG antagonist activity recognized in the mesenteric vascular preparation [86]. CQ suppressed the production of PGD_2 and PGE_2 in a dose-dependent fashion. This suppression was due to a cyclooxygenase inhibition, since the formation of the prostaglandins from exogenous endo-peroxide PGH_2 was unaffected.

CQ is an inhibitor of the cutaneous cyclooxygenase, and this effect may contribute to its anti-inflammatory action in various dermatological disorders [87].

Many researches find that using Chloroquine for RA treatment can reduce the infiltration in joints as well as the general pain, and can increase the physical function of the patients [88].

2.3. Anti-Atrial Fibrillation

Atrial fibrillation (AF) is the most heart rhythm abnormality, its incidence may elevate with age [89] [90]. AF is defined as a supraventricular tachyarrhythmia as a result of uncontrolled atrial activation with atrial mechanical function deterioration [91]. The electrocardiographic findings show the alteration of P-waves with fibrillatory or oscillatory waves of various amplitudes, sizes and timing. AF is responsible for significant mortality and morbidity cases as a result of cardiac function impairment and increasing the rate of stroke risk.

Many studies suggest that blocking the inward rectifiers through a specific condition, it become useful antiarrhythmic therapy for atrial and ventricular tachy-arrhythmias [92] [93] [94]. Since 1950, Chloroquine was noticed to have a potent antiarrhythmic effect against atrial and ventricular tachyarrhythmia [95].

Mechanism of Anti-Atrial Fibrillation

CQ act as antiarrhythmic by mechanism of blocking the heteromers of the G-protein-gated inward rectifier potassium channel subunits Kir2.1, Kir3.1 and Kir6.2 responsible for the inward-rectifier K+ current (/K1), the acetylcholine-sensitive K+ current (/KACh), and the ATP-sensitive K+ current (/KATP) respectively. Also, it able depolarizes the RMP and increases automaticity, which can be explained by its blocking effects on /K1. The latter may enhance FDs un-

derlying a triggered activity mechanism [96].

2.4. Antihypertensive Effect

Essential hypertension is a systemic and local vascular inflammation [97]. However immune system may also participate in hypertension pathogenesis [98]. Therefore some hypertension cases are a result from some autoimmune disorders [99]. The loss of immunological tolerance may increase the possibility of hypertension [100] [101]. It is important to mention that several autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus is characterized by cardiovascular diseases like hypertension and endothelial dysfunction [102] [103].

Chloroquine had been used in treatment of many autoimmune disorders [104] [105] and currently it is stilled among the first-line therapy for these conditions [106]. Chloroquine may have very promising results in patients with hypertension associated with some autoimmune disease [107].

Mechanism of Antihypertensive Effect

According to Cameron G. McCarthy *et al.* (2017), Chloroquine having different novel anti-hypertension mechanism in vasculature of spontaneously hypertensive rats, which consist of inhibition of cyclooxygenase-dependent contraction to acetylcholine, reduction of vascular and systemic generation of reactive oxygen species (ROS), improvement of nitric oxide bioavailability, and decreasing the matrix metalloproteinase enzyme (MMP2). All of these mechanisms collectively could reduce blood pressure and ameliorate the hypertensive vascular dysfunction [108] [109].

2.5. Hypoglycemic Effects

Diabetes mellitus (DM) defines as a chronic metabolic disease due to defect in insulin secretion [110], it characterized by permanent rising of blood sugar. DM affects millions of people in the world despite the presence of many anti-diabetic agents [111] [112].

Many studies proved that CQ and HCQ have beneficial antidiabetic effects. The anti-diabetic effect of them was firstly diagnosed in 1984 in patients with type 2 diabetes mellitus, when it showed a great reduction in the insulin dose required [113]. Moreover, a long term treated with CQ was found to be beneficial to reduce glycated hemoglobin (HbA1C) in diabetic patients [114].

Mechanism of Hypoglycemic Effects

CQ can inhibit insulin degradation in a way which enhances its own metabolic effect and sensitivity [115] [116]. Its main role in metabolism of insulin is through augments the connection between insulin and its receptor (tyrosine kinase), the half-life of insulin receptor complex and prologs the activity insulin [117] [118]. According to different studies about this subject, it has different effects on insulin metabolism. Thus in diabetes mellitus1 (DM1) CQ can improve

glucose tolerance [119], elevate peripheral glucose disposable and reduce insulin metabolic clearance rate [120]. While in the case of diabetes mellitus 2 (DM2), it is able to decrease the insulin resistance [121] by inhibiting degradation of the latter. The closest explanation to truth for glucose-lowering effect of this agent is that CQ can stabilize intracellular lysosome and slow the breakdown of bond between insulin and its receptor [122]. CQ is an acid trophic molecule, therefore when intracellular lysosomal concentration becomes high with it, then the intracellular pH value increased thus will produce inactivation of proteolytic enzyme (insulinase) which responsible for both insulin degradation and producing recirculation of substantial proportion of insulin in its active form [123] [124]. CQ also can improve insulin sensitivity and decrease its resistance through indirect effect of reducing inflammation [125]. Moreover, CQ was reported to have good effects in enhancing insulin sensitivity by activation of protein kinase B resulting in an increase of glucose uptakes and glycogen synthesis [126].

2.6. Anti-Lipidemic Effect

Dyslipoproteinemia is the major factor in the development of atherosclerotic process in SEL. Hyperlipidemia seems to be a common finding since it has been detected in many cases of SLE [127] [128]. Nephrotic syndrome and renal failure are the secondary cause of lipoprotein abnormalities because they can induce disturbances in lipid metabolism pathways. There are many evidences that demonstrate the effects of CQ on lipid metabolism [129]. CQ shows an effective inhibitory action on cholesterol synthesis [130].

Mechanism of Anti-Lipidemic Effect

There are several mechanisms that CQ can use to produce lipid-modifying effect. CQ could reduce the LDL (low density lipoprotein) serum level through up-regulation of LDL-C receptors that may cause an enhancement to remove plasma lipoprotein [131] [132] [133]. Many studies have reported that the favorable effects of CQ on serum lipid levels manifested by; reducing LDL-C, total cholesterol (TC), increasing in high-density lipoprotein (HDL-C), and decreasing in triglyceride level (TGs) [134] [135] [136] [137].

Reduction of Apolipoprotein b lipoprotein is investigated through using this agent as a treatment with RA and SEL treated patients [138]. One of them indicates that because it is a weak base compound, that makes it able to accumulate in high amount inside the acid intracellular organelles such as lysosomes [139] and cause a reduction in secretion of VLDL which is one of a lysosomal function. In addition, this agent inhibits the enzyme involved in cholesterol biosynthesis pathway (2, 3 oxidosqualene cyclase) [140]. CQ enhances LDL receptors activity by inhabitation of lysosomal hydrolysis of cholesterol esters. In animal model, there was a suggestion that this medicine may produce antithrombotic effects [141].

The mechanism of action of CQ may be also related to interfering action with

lysosomal activity, inhibition of antigen presentation and toll-like receptor signaling [142]. On the basis of these mechanisms of actions of this drug, the experimental data suggest that it can produce productive effects on cardiovascular disease. Indeed, its action on the lysosome able to decrease insulin degradation levels [143] and overcome cholesterol synthesis [144]. CQ can also elevate the level of LDL receptors in the liver, as a result, increasing the catabolism plasma LDL and lowering the plasma cholesterol concentration [145].

2.7. Antimicrobial Effects

2.7.1. Antimalarial Effect

CQ was registered during the first part of the 20th century as an effective quinine subunit and the drug of choice to treat malarial infection [146]. It was approved to be the most effective and successful antimalarial agent according to worldwide scale because the wide deployment coinciding with the geographical distribution of Plasmodium and it has a high efficacy against parasitic infection toxicity [147].

CQ also gained an interest in the field of other infectious diseases [148]. *In-vitro* data suggest the concept by which this agent can produce effects against all intracellular organisms, which can multiply and grow inside the acidic environment [147].

1) Mechanism of antimicrobial effect

There are multiple mechanisms of action for CQ for different microbial infections but they are varying according to the pathogens, although they do not have been improved for all pathogens, CQ enters cells as a non-protonated form where it becomes protonated according to Henderson-Hasselbach law in a reverse way to the pH [149]. So CQ becomes concentrated inside acidic organelles like Golgi vesicles, endosome, and lysosome [148]. There are two main mechanisms of action of CQ as antimicrobial agent, first, is the alkalinisation of acid vesicles inside cells that is infected by intracellular microorganisms like bacteria and fungi. Second, is the alteration of post-translation changes of newly synthesized protein in cells that infected by viruses.

2.7.2. Anti-Intracellular Parasites

The evidence of using CQ in treating infections other than malaria was described the first time *in vitro* and *in vivo* with Q fever model caused by *Coxiella burnetii* (*C. burenti*). Also, CQ is very harmful to different intracellular bacterial growths such as *T. whipplei* and *Legionella pneumophila* and others [150] [151].

There are a wide number of suggestions about the environment of low pH within the phagosomal compartments of the cell, which is the most important condition for high number of intracellular pathogens to access iron of cell to their growth and multiply [152] [153].

Mechanism of action of CQ in cellular biology, initially by manipulation of the pH of acidic vacuoles, in which, these intracellular parasites multiply, growths and lives.

Other types of bacteria like *Legionella pneumophila* and *Tropheryma whipplei* (the microbe of Whipple disease which able to multiply inside phagosomes), are inhibited by CQ since an increasing the intravascular pH will reduce the viability of this bacteria [154].

Francisella tularensis, which is the pathogen responsible for tularemia, it had been shown to be dramatically inhibited by CQ *in vitro* by the effect of this agent through mechanism of dose-dependent manner [153].

Regarding to Mycobacterium species, Chloroquine can inhibit its growth by increasing the intracellular alkalinity and decrease the level of iron availability as so it does with *L. pneumophila* [152].

2.7.3. Extracellular Infections

In case of *Staphylococcus aureus* and other some bacterial species, the addition of Chloroquine (a lysosomotropic alkalinizing agent) enhance the intracellular killing ability of some antibiotics like levofloxacin and moxifloxacin. CQ can enhance the bactericidal activity and potency of levofloxacin and moxifloxacin when their pH is neutralized from 5 to 7.4. It was reported that the low PH of intra-phagolysosomal can affect the ability of these antibiotics to kill intracellular bacteria, and this also includes other bacteria like *Salmonella enterica*, *Escherichia coli*, *Bacillus anthracis*, *Brucella abortus*, and many others [155] [156].

2.7.4. Fungal Infections

CQ showed effectiveness as antifungal against fungal infection like *Histopasma capslatum*, and *Cryptococcus neoformans*.

There are some different mechanisms of action of CQ according to fungus type. *H. capslatum* is survived inside mammalian phagolysosome and maintained the phagosomal PH of 6.5 [157] through inhibiting phagolysosomal fusion [158] and buffering the phagosomal PH [159], that would cause a restriction in iron concentration within the phagolysosome [160]. It can kill *C. neoformans* by mechanism independent of iron deprivation [161] [162]. Although, *C. neoformans* can maintain the phagolysosomal PH at 5.1 [163], treatment with CQ can cause an increase in the phagolysosomal pH that will cause an inhibition to its growth at alkaline PH [162]. CQ has an ability to kill the *Aspergillus fumigatus* using PH dependent mechanism [163], and inhibit growth of *Penicillum marneffei* [161] (an opportunistic fungus in acquired immune deficiency syndrome (AIDS) patient) by elevation the intra-vacuolar pH and making some disruptions in metabolic processes [164] [165]. The reduction in intracellular iron level results in an impaired function of many cellular enzymes that will lead to subsequent deleterious effects on major and essential steps of biological and metabolic processes such as DNA cellular replication or gene.

2.7.5. Antiviral Activities

Chloroquine also have antiviral activity exerted by increasing pH degree within acidic organelles like lysosomes, endosomes, and Golgi vesicles, this action can appear by either one form of two mechanism chooses; firstly it might responsible

for inhibition the viral important and critical steps, that low pH-dependent required for viral entry to the host cells. Indeed, there are many viruses that have PH-dependent conformational alterations that stimulate fusion, penetration and un-coating, and it is crucial for endocytosis because of the acidification that occurs inside endosomal pathway [166]. Thus the antiviral effect done by this mechanism is related to types of viruses that use endosomes for cell entry [167]. According to [168], Chloroquine, by raising the lysosomal PH above the level required can inhibit the un-coating step, which is the most essential step in induction fusion between lysosomal membrane and viral envelop of influenza B virus and hepatitis A virus (HAV) [169], because it is a pH-dependent step. Secondly, it has an ability to inhibit viral envelops glycoprotein post-translational modifications by glycosyl transferases and protease inside endoplasmic vesicle and trans-Golgi network [170] [171]. These enzymes are needed low pH values for their activation and function, therefore the administration of this medicine might lead to reducing viral infectivity by impairing the maturation of viral envelop like Flaviviridae viruses [172]. Relative to its effectiveness against HIV-1 activity, Chloroquine is making an alteration to the glycosylation pattern and to the charges of amino acid in several regions of glycoprotein (gp 120) [173] [174]. The alteration of immune escaping and broadening of antibody repertoire can be provided by reducing the number of potential N-linked glycosylation sites inside the V3 region of gp120 [174]. CQ can reduce the infectivity of HIV-1 newly produced and the ability of that virus-infected cell to form syncytia which have a relation with structural modification in gp120. CQ may be responsible for biosynthesis inhibition of sialic acid (component of HIV-1 envelop glycoprotein) by inhibition of some specific cellular enzymes that have been involved in the sialic acid biosynthesis pathway [175].

Chloroquine may also have indirect antiviral effects by preventing the spread of severe acute respiratory syndrome (SARS) associated coronavirus (CoV) in cell culture through interfering with terminal glycosylation of cellular receptor, angiogenesis converting enzyme2 (ACE2) [176], and sialic acid (a component of SARS-CoV and orthomyxoviruses receptors [177]. Moreover, it has immune-modulatory effects, where they cause decreasing the production of tumor necrosis factor α and interleukin6, which enhance the inflammatory reactions of many viral infections [178]. Chloroquine decreased viral infectivity by impaired envelop maturation like Flaviviridae viruses (172]. The anti-HIV-1 activity is through alteration of the glycosylation pattern and amino acid charge within several regions of the gp120 viral envelops protein [173] [174].

2.7.6. CQ and Covid-19

Coronaviruses are big enveloped, single-stranded, RNA viruses. Coronaviruses belong to *Coronaviridae* family which is classified into three groups according to serologic and genetic relationships [179]. The severe acute respiratory syndrome coronavirus (SARS-CoV) belongs to members of group2 [180]. The world is currently in the throes of a pandemic of this kind of coronavirus which is com-

mon as COVID-19. The ability of Chloroquine to inhibit certain types of Coronaviruses has been explored with excellent results [181] [182].

Several *in vitro* studies report antiviral activity of Chloroquine and hydroxychloroquine against SARS-CoV-2. *In vivo* data, although promising, is currently limited to one study with considerable limitations. CQ and HCQ are incorporated in many available protocols guidelines for the treatment of COVID-19 [183]. The efficacy of hydroxychloroquine was improved by combining this drug with azithromycin (an antibiotic) with antiviral properties against other RNA-viruses such as Zikavirus [184]. Also, CQ and HCQ are listed with drugs which may be useful in prophylaxis of COVID-19 [185]

1) Mechanism of CQ/HCQ in treatment of COVID-19

Many Postulates describe the potential mechanisms of action of CQ/HCQ against SARS-CoV-2. CQ may reduce glycosylation angiotensin-converting enzyme 2 (ACE2) by binding to (ACE2) on the cell surface virus to enter the host cells [176]. ACE2 expression is also believed to be up regulated by infection with SARS-CoV-2 [186]. Other hypothesis postulates that CQ might block the production of pro-inflammatory cytokines (such as interleukin-6); thereby blocking the pathway that subsequently leads to acute respiratory distress syndrome (ARDS) [188]. In addition to the fact that some viruses enter host cells through endocytosis using vesicles called endosomes. Virus can replicate through endosomes and released when endosome fuses with the acidic intracellular lysosome. The release of virus is essential for viral replication when endosomes ruptured [187]. The rupture of endosomes is blocked by Chloroquine, which accumulates in lysosomes, interfering with this process [188]. It also believed that Chloroquine raises the pH level of the endosome, which may interfere with virus entry and/or exit from host cells [189]. Future studies may show and clarify the effectiveness and precise mechanism of action of CQ/HCQ in the treatment of COVID-19.

2.8. Systemic and Dermatological Disease

CQ and HCQ were used to treat a variety of skin conditions, the scientific evidence being insufficient and just limited to some isolated case reports. Its usage is recommended in patients with disseminated granuloma annular that does not show a good response or only limited response to topical corticosteroids [190]. Both CQ and HCQ showed an efficacy for long treatment of photosensitive disorders, like actinic recticuloid and chronic actinic dermatitis [191]. CQ and HCQ prevent the progression of graft-versus-shot disease (GVHD) by suppression of T cells response to foreign antigens and alteration in T cells production of pro-inflammatory cytokines, such as IL-1, IL6 and TNF-alpha [192].

HCQ is the drug of choice in Patients with localized cutaneous disease who fail to respond to sun protection and topical or intralesional corticosteroid therapy or those with alopecia or disseminated skin lesions [193]. It also effective for other photosensitivity dermatoses like porphyria cutanea tarda (PCT) [194] polymorphous light eruption [195], dermato-myositis (skin manifestations) [196], reticular erythematous mucinosis [197], essner's lymphocytic infiltrate [198] and

solar urticarial [199], especially in the summer months for patients who fail to respond to sun protection or "hardening" with light therapy [200]. CQ and HCQ are reported to be effective for granulomatous dermatoses, such as sarcoidosis (with neurologic involvement) [201] and disseminated granuloma annulare [202], and may even be used intralesionally [203]. Patients with lymphocytoma cutis, atopic dermatitis, urticarial vasculitis, localized scleroderma, and idiopathic panniculitis have also been treated with CQs [204].

3. Adverse Effects of Chloroquine (Toxicity)

Chloroquine when used in standard low doses shows only a few adverse effects, especially when used as prophylaxis for malaria or other systemic disorders. However, acute toxicity by CQ is most frequently encountered if it is given very rapidly by parenteral routes either in therapeutic or overdose. The most common side effects of CQ are retinopathy, neuromayopathy, myopathy, and cardiomyopathy [205] [206] [207].

3.1. Adverse Effects on the Eye

It includes two common adverse effects which are; retinopathy and keratopathy. Both of them are associated with long-term administration of CQs [205] [206].

3.2. Adverse Effects on the Ears

Ears' adverse reaction of CQs is associated with reversible ototoxicity. Sensorineural hearing loss, a sense of imbalance, and tinnitus were reported [208] [209].

3.3. Adverse Effects on the Cardiovascular System

Chloroquine rarely caused cardiovascular side effects, but it may cause severe and irreversible disorders like cardiomyopathy and conduction disturbances [207] [208] [209] [210]. Hemolysis and blood dyscrasias may be rarely occurred [211].

3.4. Adverse Effects on the Digestive System

Gastrointestinal discomfort is the most common side effects of Chloroquine. It may be mild to moderate and can be managed by dose reduction. Nausea, vomiting, and diarrhea are the other common gastrointestinal event also might be happened [212] [213].

3.5. Adverse Effects on the Skin

Dermatological adverse reaction related to Chloroquine is pruritus, which is appeared more common in dark-skin patient received this agent, because it binds to melanin in the skin [214].

3.6. Adverse Effects on the Musclo-Skeletal System

Musculo-skeletal system adverse Chloroquine reaction is a myopathy which re-

sponsible for muscle weakness, decreased or loss of tendons reflexes [215].

3.7. Adverse Effects on the Nervous System

Nervous system Chloroquine's most common adverse effect is a neuromyopathy which is characterized by slowly progressive weakness when it is used for a long time especially in the old patients [216]. Metabolic adverse effect is characterized by hypoglycemic effect; this may lead to convulsion [217].

4. Conclusion

Chloroquine antimalarial agents saved the lives of many people in the whole world. It was firstly used almost a century ago, and it is not only used to treat the malarial infection but also it can be used in a variety of autoimmune, inflammatory disorders and microbial infections. In this review, data were collected to demonstrate the multiplicity actions displayed by Chloroquine to improve and treat different inflammatory diseases, immune system disorders, microbial infections and several metabolic disturbances. There is also a role in the recovery of some skin diseases. Through their mechanism, the CQ can produce its action which is demonstrated briefly. Also, toxicity and adverse effects of CQ were showed in this review. Low doses of CQ may be accompanied by low side effects. The relation and benefits of CQ in the treatment of Covid-19 also still need more studies to clarify the mechanism and when it is useful and when it should be arrested. In conclusion, CQ is a drug of wide applications and needs more studies to precisely determine the exact mechanisms of action that happen by its effect and to develop strategies that will help to be used in the clinic.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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