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Antibacterial, antiviral, and antifungal activities of quinine and its derivatives: A narrative mini-review

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ABSTRACT

Quinine sulfate, the main active compound from quinine extract, has been applied as an old drug under the category of a limited over-the-counter drug. This compound is a medication used commonly to treat malaria. This includes the treatment of malaria caused by *Plasmodium falciparum* which is resistant to chloroquine when artesunate is not available. In addition, quinine and its derivatives showed antibacterial, antifungal, and antiviral activities. Microbial resistance to quinine occurs in certain areas of the world. In addition, quinine can affect kidney function, hematology, cardiovascular function, and liver function as the major side effects. Novel biocompatible micro and Nano formulations are needed to overcome these disadvantages. The present mini-review has tried to address these formulations considering their antimicrobial activities.

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Introduction

Quinine ($C_{20}H_{24}N_2O_2$) is an alkaloid, a naturally occurring chemical compound (Figure 1) [1]. It has been showed that the bark of *Remijia* and *Cinchona* genera contains a suitable percentage of quinine [2, 3]. Also, several therapeutic and curative effects including antiparasitic, antibacterial, antiviral, antifungal, and anticancer activities have been found for quinine and its analogs [1, 4, 5]. However, the cytotoxicity of this compound leads to some side effects such as headache, ringing in the ears, vision issues, low blood platelets, an irregular heartbeat, and sweating [6]. It is unclear if use during pregnancy causes harm to the baby, treating malaria during pregnancy with quinine when appropriate is still recommended. How it works as a medicine is not entirely clear. As we know there are some subgroups of heterocyclic alkaloids such as Imidazoles, piperidines, purines, isoquinolines, tropanes, quinolizidines, pyrrolidines, and pyrrolizidines. (Figure 2) [7]. Effective biocompatible micro and nanoformulations based on organic and inorganic nanomaterials such as lipid and metallic nanoparticles are required to reduce the systemic toxicity of quinine [8-10]. This mini-review has tried to discuss progress and challenges in novel formulations of quinine with antibacterial, antiviral, and antifungal activities.

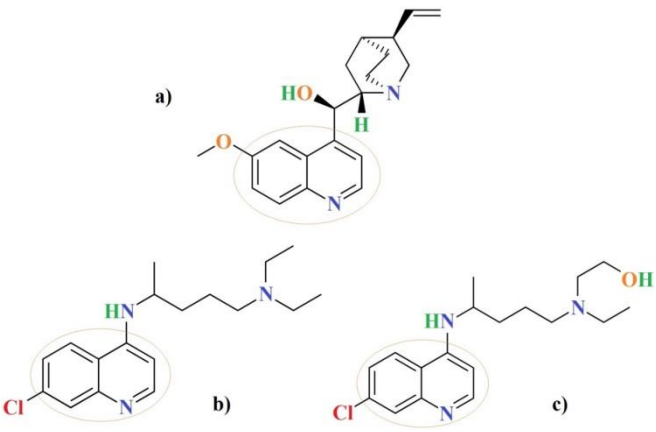

Fig. 1. Chemical structure of quinine (a) , chloroquine (b) , and hydroxychloroquine (c).

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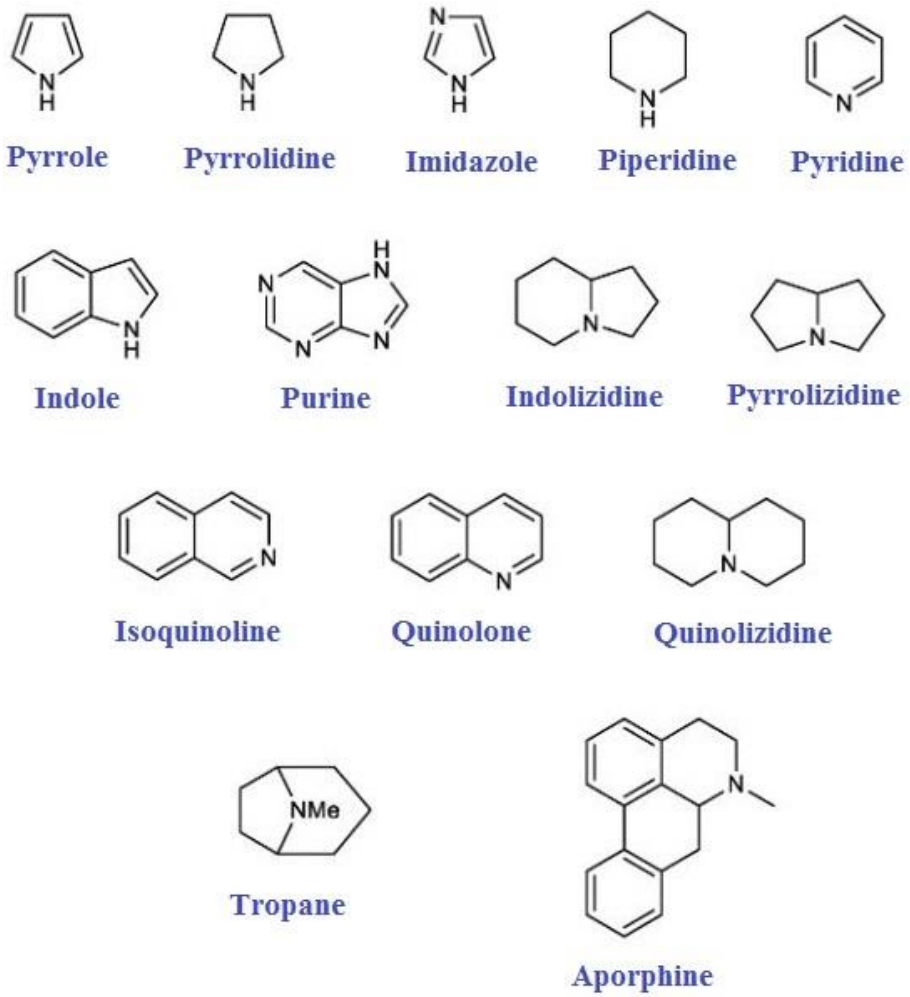

Fig. 2. Heterocyclic alkaloids can be classified into 14 subgroups [7].

Antibacterial activity

Drugs with cationic amphiphilic properties can interact with membrane phospholipids by electrostatic interaction between the cationic nitrogen and the negatively charged phosphate of the phospholipid head group [11, 12]. Besides, drug pharmacodynamics and pharmacokinetics can be affected by cationic amphiphilic compounds. Significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) was found for amphiphilic cationic quinine-derived [13]. The availability of antibiotics has led to many bacterial strains becoming resistant to them, making antimicrobial resistance one of the most pressing problems facing humanity today. Therefore, finding new antimicrobial agents is of utmost importance, especially from traditional medicinal plants and their derivatives, the antimicrobial properties of some quinine esters have been demonstrated in a screening study of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus substillis*. Due to their potential antimicrobial activities, these compounds could be used against both Gram-negative and Gram-positive bacteria [14]. Quinine can bind heme and has antimalarial effects in Plasmodium spp. This alkaloid can inhibit heme's interaction with DOCK8 (dedicator of cytokinesis 8) protein for bacterial host clearance [15, 16]. Due to the common side effects of quinine for malaria treatment, modified quinine-based derivatives have been developed. They are also antimalarial drugs, but they are more potent and have less potential for side effects [17].

Literature indicates that quinine derivatives inhibit *S. aureus*, *Streptococcus pneumoniae*, *P. aeruginosa*, and *E. coli*. DNA synthesis is inhibited by quinoline derivatives, resulting in bacterial cell death as DNA gyrase is cleaved. The ability of compounds in the quinoline series, such as those used to prevent

pathogenic processes in the body, particularly those caused by *S. aureus*, to participate in the irreversible suppression of transpeptidase activity, is not yet fully understood, Molecularly identified a penicillin-binding protein that catalyzes peptidoglycan synthesis, an essential component of bacteria's cell wall, contributes to pathogen death [17]. Some bacteria that infect the skin were reported to be inhibited by quinine sulfate. In addition, the significant antibacterial activity of amphiphilic, cationic, and quinine-derived compounds against most pathogenic bacteria, including MRSA, has been reported [18].

Antiviral activity

The first study about quinine's efficacy as an antiviral agent was done in 1946 by Seeler and coworkers. This study concluded that quinine has an antiviral effect against the influenza virus by consistently slowing the course of influenza virus infection [19]. Quinine sulfate has a chemical structure (Figure 1) and mechanism similar to chloroquine and hydroxychloroquine, which can bind to the Lys353 residue in the peptide domain of the angiotensin-converting enzyme 2 (ACE-2) receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The most common bioactive compounds isolated from the *Cinchona* genus related to Rubiaceae family are quinidine, quinine, cinchonidine, and cinchonine [20]. The outbreak of dengue virus (DENV) from the Flaviviridae family continues to develop globally with associated mortality and substantial monetary burden, however, no treatment has been accepted to combat the virus. A study evaluated four drugs approved by the Food and Drug Administration (FDA), including aminolevulinic acid, azelaic acid, mitoxantrone hydrochloride, and quinine sulfate, which tested its ability to inhibit DENV replication. Quinine inhibited the production of DENV by about 80% compared to untreated controls, while the other three drugs reduced the production of the virus by about 50%. These results show how effective quinine is at stimulating antiviral genes to reduce DENV replication [21].

Few studies have investigated the role of quinine in the treatment of malaria in human immunodeficiency virus (HIV)-infected populations. The first study, conducted in the Congo in 1986, showed a 92% cure rate for malaria in HIV-infected patients treated with oral quinine, with similar results in HIV-negative patients. In Nigeria, coadministration of nevirapine and quinine significantly decreased plasma levels of quinine and increased plasma levels of 3-hydroxyquinine ($C_{20}H_{24}N_2O_3$), the major metabolite of quinine [22]. A study showed that quinine in Vero cells inhibited SARS-CoV-2 infection more effectively compared to chloroquine and hydroxychloroquine, which was less toxic. Quinine also exhibited antiviral activity in human Caco-2 colonic epithelial cells and the lung cell line A549, which stably expresses ACE2 and trans-membrane protease serine 2 (TMPRSS2) [23].

A molecular docking study determined the interaction between SARS-CoV-2 and quinine derivative compounds. The results showed that of the 10 compounds tested against SARS-CoV-2 virus cells, all, including quinine, were capable of acting as antiviral agents [24]. Antiviral activity of quinine and its derivatives has also been demonstrated in several other viruses, including H1N1 [25], HIV, influenza A virus, Zika virus, Ebola, and dengue [26-28].

Recent studies indicated the main antiviral mechanism of quinine as the indirect killer of viruses. Previous studies have examined the significant antiviral effect of quinine sulfate on cells infected with the dengue virus. As a relative similarity between the SARS-CoV-2 and dengue virus structures, SARS-CoV-2 may apply certain similar ways to infect the cell and trigger cytokines to fight the virus (Figure 3). Virus-infected host cells cause viral RNA to break out and interfere with normal protein synthesis. However, in infected host cells, increased expression of the pathogen recognition receptor of retinoic acid-inducible gene I (RIG-I) [29]. Moreover, this alkaloid as an immunostimulator induces the production of interferon-alpha (IFN-α) cytokines against viruses [30]. Quinine significantly suppresses the synthesis of HSV-1 proteins, inhibiting the first stages of the influenza A (H1N1) replication cycle [31]. It has been suggested that quinine exerts its anti-viral effect by indirectly acting on host cells by inducing a cellular defense mechanism, which may interfere with multiple events throughout the virus replication cycle. In addition to quinine-induced kappa-B nuclear factor (NF-kB) inhibition, this metabolite can inhibit gene expression and results in a significant reduction in viral infection [26]. Also, quinine has proven antiviral effects against the herpes simplex virus (HSV) [32].

Antifungal activity

Quinoline can cause changes in the cell membrane permeability, loss of mitochondrial membrane potential, accumulation of reactive oxygen species (ROS), and effective inhibition of germination and formation of *S. sclerotiorum sclerotia* [1]. Systemic toxicity of quinine can be reduced by conjugation of the triazole moiety with quinine. Quinine-triazole hybrid exhibited a remarkable antifungal effect at micromolar amounts compared to reference drugs. Minimum inhibitory concentrations (MICs) were 121.3, 112.7, and 119.4 µM/mL against *Aspergillus clavatus*, *Aspergillus niger*, and *Candida albicans* respectively for this quinine derivative [33].

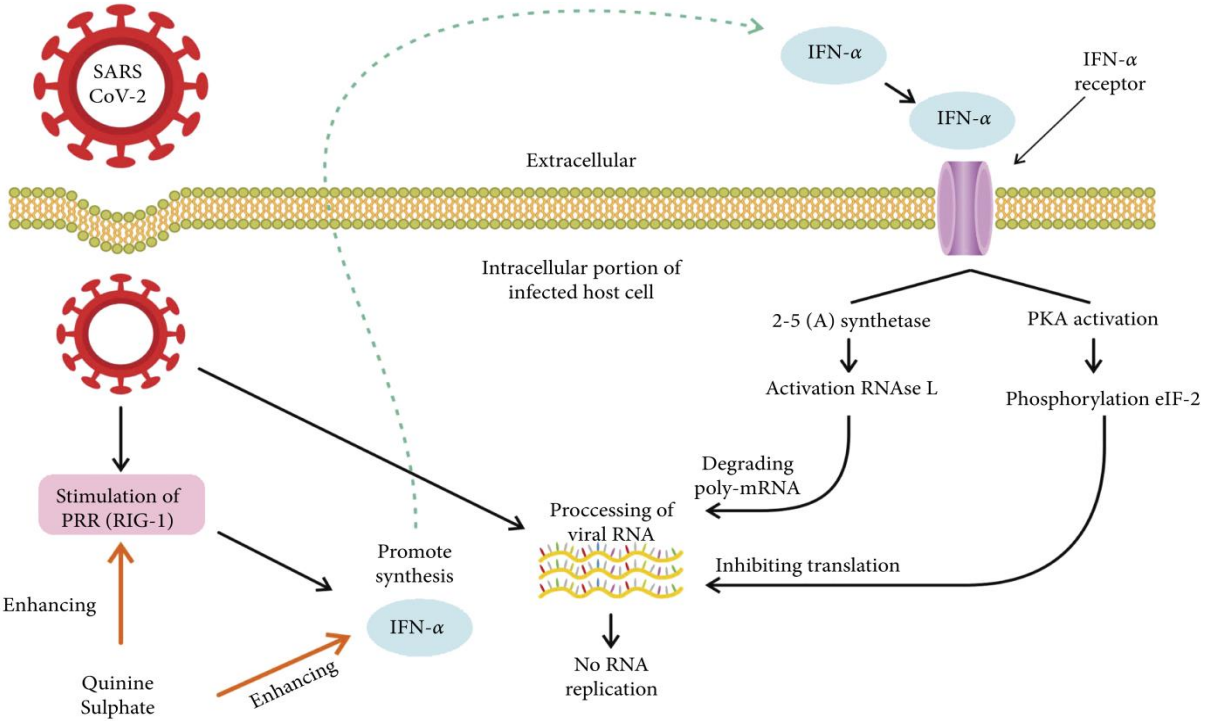

Fig. 3. Mechanism of quinine sulphate as an antiviral agent (extracted from [29]).

Conclusions

Quinine and its derivatives can inhibit DNA synthesis and lead to bacterial cell death as DNA gyrase damage. Indirect killing of the virus has been found as the major antiviral mechanism of quinines. In addition, as an immunostimulator, this alkaloid increases the production of IFN-α cytokines against viruses. As the main antifungal mechanisms, changes in the cell membrane permeability, accumulation of ROS, loss of mitochondrial membrane potential, and effective inhibition of germination and formation of fungi have been found for some quinoline derivatives. Cationic amphiphilic derivatives of quinine can interact with phospholipids of the membrane via electrostatic interaction between the cationic nitrogen and the negatively charged phosphate of the phospholipid head group.

Study Highlights

- DNA synthesis of Gram-negative and Gram-positive bacteria can be inhibited by quinine and its derivatives.
- Quinine can increases the production of IFN-α cytokines against viruses.
- Changes in the cell membrane permeability, accumulation of ROS, and loss of mitochondrial membrane potential have been recognized for some quinoline derivatives.

Abbreviations

ACE-2: Angiotensin-converting enzyme 2
DENV: Dengue virus
DOCK8: Dedicator of cytokinesis 8
FDA: Food and drug administration
HIV: Human immunodeficiency virus

HSV: Herpes simplex virus
IFN-α: Interferon-alpha
MICs: Minimum inhibitory concentrations
MRSA: Methicillin-resistant *Staphylococcus aureus*
RIG-I: Retinoic acid-inducible gene I
ROS: Reactive oxygen species
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions
All authors: conceptualization, preparing the first draft, and editing.

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References
1. Yang G-Z, Zhu J-K, Yin X-D, Yan Y-F, Wang Y-L, Shang X-F, et al. Design, Synthesis, and Antifungal Evaluation of Novel Quinoline Derivatives Inspired from Natural Quinine Alkaloids. Journal of Agricultural and Food Chemistry. 2019;67(41):11340-53. doi:https://doi.org/10.1021/acs.jafc.9b04224
2. Ruiz-Mesia L, Ruiz-Mesía W, Reina M, Martínez-Diaz R, de Inés C, Guadaño A, et al. Bioactive Cinchona Alkaloids from Remijia peruviana. Journal of Agricultural and Food Chemistry. 2005;53(6):1921-6. doi:https://doi.org/10.1021/jf048880e
3. Latarissa IR, Barliana MI, Meiliana A, Lestari K. Potential of Quinine Sulfate for COVID-19 Treatment and Its Safety Profile. Clinical Pharmacology: Advances and Applications. 2021:225-34. doi:https://doi.org/10.2147/CPAA.S331660
4. Akhtar N, Pradhan N, Barik GK, Chatterjee S, Ghosh S, Saha A, et al. Quinine-Based Semisynthetic Ion Transporters with Potential Antiproliferative Activities. ACS applied materials & interfaces. 2020;12(23):25521-33. doi:https://doi.org/10.1021/acsami.0c01259
5. Olateju OA, Babalola CP, Olubiyi OO, Kotila OA, Kwasi DA, Oaikhena AO, et al. Quinoline Antimalarials Increase the Antibacterial Activity of Ampicillin. Frontiers in Microbiology. 2021;12. doi:https://doi.org/10.3389/fmicb.2021.556550
6. Kayser O, Kiderlen AF, Croft SL. Natural products as potential antiparasitic drugs. In: Atta ur R, editor. Studies in Natural Products Chemistry. 26: Elsevier; 2002. p. 779-848. doi:https://doi.org/10.1016/S1572-5995(02)80019-9
7. Casciaro B, Mangiardi L, Cappiello F, Romeo I, Loffredo MR, Iazzetti A, et al. Naturally-Occurring Alkaloids of Plant Origin as Potential Antimicrobials against Antibiotic-Resistant Infections. Molecules. 2020;25(16):3619. doi:https://doi.org/10.3390/molecules25163619
8. Ahmadi S, Javid H. Novel formulations of ellagic acid for the improvement of antimicrobial, antioxidant, anticancer, antidiabetic, and neuroprotective applications. Nano Micro Biosystems. 2023;2(1):31-5. doi:https://doi.org/10.22034/nmbj.2023.388479.1015
9. Ahmadi S, Emamirad S. Recent progresses and challenges in formulations of vincristine and its derivatives for hindering cancer cells. Nano Micro Biosystems. 2023;2(1):36-41. doi:https://doi.org/10.22034/nmbj.2023.389869.1017
10. Karimi S, Heidari F, Amraei S. Therapeutic aspects of berberine and its derivatives: recent advances and challenges. Nano Micro Biosystems. 2023;2(1):42-7. doi:https://doi.org/10.22034/nmbj.2023.390449.1018
11. Do TTT, Dao UPN, Bui HT, Nguyen TT. Effect of electrostatic interaction between fluoxetine and lipid membranes on the partitioning of fluoxetine investigated using second derivative spectrophotometry and FTIR. Chemistry and Physics of Lipids. 2017;207:10-23. doi:https://doi.org/10.1016/j.chemphyslip.2017.07.001
12. Uppu DSSM, Konai MM, Baul U, Singh P, Siersma TK, Samaddar S, et al. Isosteric substitution in cationic-amphiphilic polymers reveals an important role for hydrogen bonding in bacterial membrane interactions. Chemical Science. 2016;7(7):4613-23. doi:https://doi.org/10.1039/C6SC00615A
13. Lv J, Qian Y, Liu T, Wang Y. Synthesis and evaluation of amphiphilic cationic quinine-derived for antibacterial activity against methicillin-resistant Staphylococcus aureus. Bioorganic & Medicinal Chemistry Letters. 2007;17(15):4102-6. doi:https://doi.org/10.1016/j.bmcl.2007.05.065
14. Mukusheva GK, Zhasymbekova AR, Seidakhmetova RB, Nurkenov OA, Akishina EA, Petkevich SK, et al. Quinine Esters with 1,2-Azole, Pyridine and Adamantane Fragments. Molecules. 2022;27(11). doi:https://doi.org/10.3390/molecules27113476
15. Martins R, Maier J, Gorki AD, Huber KV, Sharif O, Starkl P, et al. Heme drives hemolysis-induced susceptibility to infection via disruption of phagocyte

functions. Nature Immunology. 2016;17(12):1361-72. doi:https://doi.org/10.1038/ni.3590
16. Leanse LG, Dong PT, Goh XS, Lu M, Cheng JX, Hooper DC, et al. Quinine Enhances Photo-Inactivation of Gram-Negative Bacteria. Journal of Infectious Diseases. 2020;221(4):618-26. doi:https://doi.org/10.1093/infdis/jiz487
17. Mukusheva G, Zhasymbekova A, Nurmaganbetov Z. Synthesis and structure of new modified derivatives based on the quinine molecule and their biological activity. Polish Journal of Chemical Technology. 3923;25(1):28-34. doi:https://doi.org/10.2478/pjct-2023-0005
18. Latorre-Sánchez A, Johansson M, Zhang Y, Malkoch M, Pomposo JA. Active quinine-based films able to release antimicrobial compounds via melt quaternization at low temperature. Journal of Materials Chemistry B. 2018;6(1):98-104. doi:https://doi.org/10.1039/C7TB02739G
19. Seeler AO, Graessle O, Ott WH. Effect of Quinine on Influenza Virus Infections in Mice. The Journal of Infectious Diseases. 1946;79(2):156-8. doi:https://doi.org/10.1093/infdis/79.2.156
20. Maldonado C, Barnes CJ, Cornett C, Holmfred E, Hansen SH, Persson C, et al. Phylogeny Predicts the Quantity of Antimalarial Alkaloids within the Iconic Yellow Cinchona Bark (Rubiaceae: Cinchona calisaya). Frontiers in Plant Science. 2017;8. doi:https://doi.org/10.3389/fpls.2017.00391
21. Malakar S, Sreelatha L, Dechtawewat T, Noisakran S, Yenchitsomanus PT, Chu JJH, et al. Drug repurposing of quinine as antiviral against dengue virus infection. Virus Research. 2018;255:171-8. doi:https://doi.org/10.1016/j.virusres.2018.07.018
22. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria Journal. 2011;10:144. doi:https://doi.org/10.1186/1475-2875-10-144
23. Große M, Ruetalo N, Layer M, Hu D, Businger R, Rheber S, et al. Quinine Inhibits Infection of Human Cell Lines with SARS-CoV-2. Viruses. 2021;13(4). doi:https://doi.org/10.3390/v13040647
24. Roza D, Selly R, Munsirwan R, Fadhilah G. Molecular Docking of Quinine Derivative as Inhibitor in Sars-Cov-2. Journal of Physics: Conference Series. 2021;1819(1):012053. doi:https://doi.org/10.1088/1742-6596/1819/1/012053
25. Bazotte RB, Hirabara SM, Serdan TAD, Gritte RB, Souza-Siqueira T, Gorjao R, et al. 4-Aminoquinoline compounds from the Spanish flu to COVID-19. Biomedicine and Pharmacotherapy. 2021;135:111138. doi:https://doi.org/10.1016/j.biopha.2020.111138
26. Abdulaziz L, Elhadi E, Abdallah EA, Alnoor FA, Yousef BA. Antiviral Activity of Approved Antibacterial, Antifungal, Antiprotozoal and Anthelmintic Drugs: Chances for Drug Repurposing for Antiviral Drug Discovery. Journal of Experimental Pharmacology. 2022;14:97-115. doi:https://doi.org/10.2147/jep.s346006
27. D'Alessandro S, Scaccabarozzi D, Signorini L, Perego F, Ilboudo DP, Ferrante P, et al. The Use of Antimalarial Drugs against Viral Infection. Microorganisms. 2020;8(1):85. doi:https://doi.org/10.3390/microorganisms8010085
28. Latarissa IR, Barliana MI, Meiliana A, Lestari K. Potential of Quinine Sulfate for COVID-19 Treatment and Its Safety Profile: Review. Clinical Pharmacology: Advances and Applications. 2021;13:225-34. doi:https://doi.org/10.2147/CPAA.S331660
29. Nugraha RV, Ridwansyah H, Ghozali M, Khairani AF, Atik N. Traditional Herbal Medicine Candidates as Complementary Treatments for COVID-19: A Review of Their Mechanisms, Pros and Cons. Evidence-Based Complementary and Alternative Medicine. 2020;2020:2560645. doi:https://doi.org/10.1155/2020/2560645
30. Latarissa IR, Barliana MI, Meiliana A, Lestari K. Potential of Quinine Sulfate for COVID-19 Treatment and Its Safety Profile: Review. Clinical Pharmacology: Advances and Applications. 2021;13:225-34. doi:https://doi.org/10.2147/cpaa.s331660
31. Abookleesh FL, Al-Anzi BS, Ullah A. Potential Antiviral Action of Alkaloids. Molecules. 2022;27(3):903. doi:https://doi.org/10.3390/molecules27030903
32. Baroni A, Paoletti I, Ruocco E, Ayala F, Corrado F, Wolf R, et al. Antiviral effects of quinine sulfate on HSV-1 HaCat cells infected: analysis of the molecular mechanisms involved. Journal of Dermatological Science. 2007;47(3):253-5. doi:https://doi.org/10.1016/j.jdermsci.2007.05.009
33. Sahu A, Agrawal R. Synthesis of Quinine-Triazole Derivatives (QNTDs) with Antifungal Potency. Anti-Infective Agents. 2022;20(3):66-70. doi:https://doi.org/10.2174/2211352520666220124101052

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