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REVIEW

Natural and Synthetic Drugs as Potential Treatment for Coronavirus Disease 2019 (COVID-2019)

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Abstract
Coronavirus disease 2019 (COVID-19) has become a global pandemic in a short period, where a tragically large number of human lives being lost. It is an infectious pandemic that recently infected more than two hundred countries in the world. Many potential treatments have been introduced, which are considered potent antiviral drugs and commonly reported as herbal or traditional and medicinal treatments. A variety of bioactive metabolites extracts from natural herbal have been reported for coronaviruses with some effective results. Food and Drug Administration (FDA) has approved numerous drugs to be introduced against COVID-19, which commercially available as antiviral drugs and vaccines. In this study, a comprehensive review is discussed on the potential antiviral remedies based on natural and synthetic drugs. This review highlighted the potential remedies of COVID-19 which successfully applied to patients with high cytopathic inhibition potency for cell-to-cell spread and replication of coronavirus.

Keywords Antivirus · Chloroquine · Dosage · Pandemic · Plasma · Ivermectin

1 Introduction

The emergence of recent coronavirus disease 2019 (COVID-19) has become an alarming issue and shaken the whole world. The new pathogenic strain [1] produced by coronavirus has infected millions of people worldwide that led to massive death since December 2019 [2]. COVID-19 was first identified in Wuhan, China from an unknown source of coronavirus, which gradually spread to the whole world [3–7] and tragically affected human life. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19 in humans and animals [8–14]. COVID-19 has a similarity with the earlier reported disease called severe acute respiratory syndrome (SARS) caused by severe acute respiratory syndrome coronavirus (SARS-CoV), regarding their symptoms i.e. cough, fatigue, fever, and lower respiratory sign [15–17]. The current pandemic has compelled the researchers to explore new effective drugs against COVID-19.

SARS-CoV-2 is structurally similar to other coronavirus and is only differentiated by the prominent spike of proteins [18]. Coronaviruses belong to positive single-strand long RNA viruses [19, 20] with numerous structural proteins i.e. envelope (E), spike (S) [21], membrane (M), nucleocapsid (N) proteins contributing or assisting virus for replication [22] and entry in the host [23]. Both SARS-CoV and SARS-CoV-2 have common angiotensin-converting enzyme 2 (ACE2) used as a receptor that is responsible for the respiratory syndrome. Startlingly, the spike-glycoprotein plays an important role for a strong guest host binding with the targets receptor [24]. The Mpro enzyme contributed to the viral replication of coronavirus [25]. The viral proteases (PL-pro and 3-CL pro) are contributed to the cleavage of replicate polyproteins, significant for viral replication [26]. SARS-CoV-2 can also enter into the host via endosomes at low pH, which can be controlled by increasing pH [27]. A comprehensive illustration of the SARS-CoV-2 structure, replication cycle and immune system response is depicted in (Fig. 1) [28, 29].

The phylogenetic tree of coronaviruses consists of four types i.e. α-coronavirus, β-coronavirus, γ-coronavirus, δ-coronavirus [30]. Phylogeny and genomic analysis

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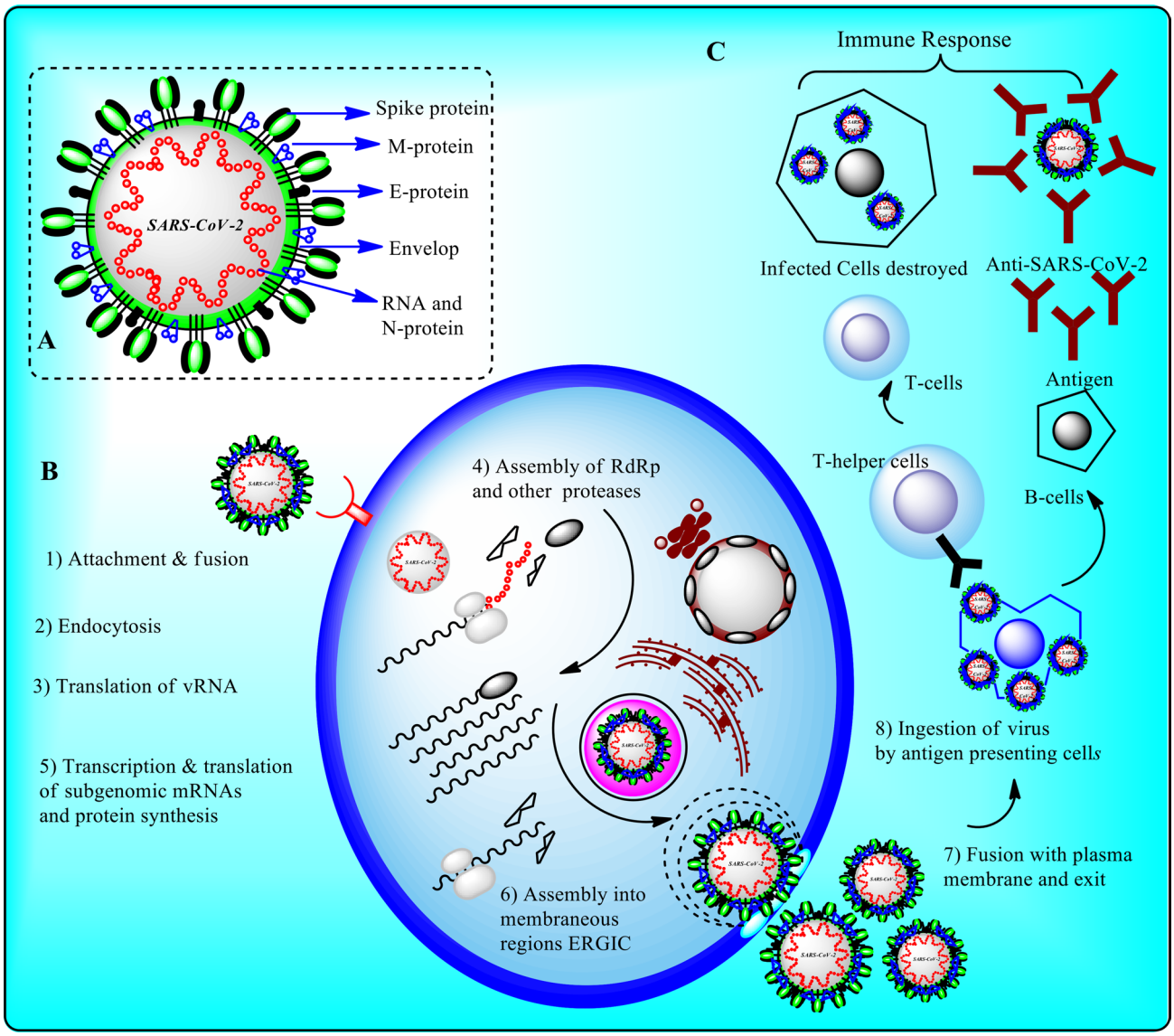


Fig. 1 Diagrammatic depiction of SARS-CoV-2 structure (**a**); replications process (**b**) and immune response (**c**)

declared SARS-CoV-2 is belonged to β-coronavirus [31, 32]. Previously reported coronaviruses such as corona-SARS [33–36], infectious bronchitis virus (IBV) [37, 38], mouse hepatitis coronavirus (MHV) [39–42], feline infectious peritonitis (FIP) [43], human immunodeficiency virus (HIV) [44] and hepatitis C virus (HCV) [45], canine coronavirus [46], which originated from different sources such as bats [47–49], chicken, pig, mouse and rat [50]. Coronavirus diseases are triggered by cytopathogenicity [51] and virus multiplication in the human body such as the respiratory tract [52, 53], intestines, kidneys and brain [54, 55], and extensively spread from human to another human. Nevertheless, coronavirus is spread via a secondary mode of transmission very quickly in numerous countries of the world. The best strategies have been imposed to reduce social contact [56–58] as well as enforcing Chinese rules and restrictions [59]. Unfortunately, the number of cases of highly contagious [60] COVID-19 is still increasing due to the fast viral replication [61], poor quarantine [62, 63] and human to human transmission [64, 65] through touching, coughing and sneezing [66, 67].

Coronavirus is mainly attacked on the respiratory system and also damages myocardial tissues [68, 69] and gastrointestinal organs [70]. Many common factors could seriously put patients at high risk such as (1) nature of drug/medicine, (2) dosage/potency of the drug, (3) condition of the patient (i.e. aging, obesity, sex [71], diabetes, kidney illness [72, 73], liver disease [74], anxiety/ stress [75], pregnancy [76]). The existing connection between diabetes and obesity contributes to significant hazardous factors impacting

the therapeutic severity of SARS-CoV-2 infections [77]. An ability to boost the body's immune system may significantly affect the medicinal remedies for COVID-19 treatment as a person to person immunity strength varies [78]. It equally affected young and old people. However, the affected ratio of females is lower compared to males due to a versatile hormonal system and immunity set up [79].

Based on literature precedent, exhaustive efforts have been carried out to produce effective antiviral drugs to control coronavirus infection and replication [80, 81] in entry host and to enhance the host immune response [82, 83] might take several years before it's become commercially available. Many reviews [84–94] reported on the types, transmission or origin of coronavirus. In this review, natural and synthetic drugs-based treatments illustrated for COVID-19 and the outcomes of their drug's potential is thoroughly discussed.

2 Types of Treatment for COVID-2019

Numerous treatment methods have been reported to cure COVID-19. Among various treatments, natural and synthetic remedies are the most commonly reported. Other strategies involved in the inactivation of pathogens especially on coronavirus infections have also been widely reported such as UV A [95], UV C light [96], heat sensitivity [97] octanoic acid treatment [98], to name a few. The photodynamic and thermodynamic treatment strategies are involved penetration of UV light/heat into the fluid of platelet and inactivation of pathogenic microorganisms and leucocytes to damage the nucleic acids from continue spreading the viral.

2.1 Natural Treatment

The natural remedy is a naturally occurring secondary metabolite extracted from living organisms such as plants, animals, fungi and bacteria having potential antiviral agents [99]. The natural remedies are remarked as virtuous sources for the development and production of antiviral agents [100, 101]. Several metabolites derived from plants and animals have been recounted with antitumor, antifungal, antiinflammatory and antiviral properties [102, 103]. In Asian countries, herbal plant treatment has been conventionally used for many pharmaceutical purposes [104].

2.1.1 Plants-Based Treatment

Many studies reported on plants based natural products as alleged remedies for viral infection [105]. The bioactive metabolites from various parts of plant extract i.e. stems, seeds, roots and leaves have been widely reported with antiviral properties. *Stephania tetrandra* or *Menispermaceae* are examples of plants with excellent sources of *bis*-benzylisoquinoline alkaloids namely fangchinoline **(1)**, tetrandrine **(2)** and cepharanthine **(3)**. Compound **(1–3)** has been reported to inhibit protein expression, repress infectivity, and inhibit the replication of coronavirus in human and virus-induced host reappearance. Natural remedies from active metabolites **(1–3)** in the plant are beneficial and convenient for potential treatment and anticipation of COVID-19 (Fig. 2) [106].

In Asia, conventional remedies based upon natural resources namely garlic, cardamom, pennyroyal, liquorice, pepper, turmeric, tragacanth and hedge nettle (Fig. 3) have been alleged for an effective cure against coronavirus diseases. Among these conventional remedies, curcumin, a secondary metabolite derived from turmeric, is more conspicuous and widely reported for potential COVID-19 treatment due to stronger interaction with protease enzyme as compared to other natural compounds (i.e. pepper, pennyroyal, tragacanth) [107].

Chinese natural remedies have been renowned as imperative traditional remedies due to high efficiency, negligible and less side effects [108]. Chinese traditional herbs often offer rapid remedies for virus outbreak. *Gancao* **(1)**, *fangfeng* **(2)**, *baizhu* **(3)**, *jinyinhua* **(4)** and *huangqi* **(5)** are examples of Chinese natural herbs that contain good antiviral potency with significant consequences (Fig. 4) [109, 110]. A commercial natural drug called Lianhua Qingwen is another Chinese herb derived from a combination of *yinhuapinggan* granule and *San Wu huangqin* decoction has been recently reported to cure COVID-19 in Beijing, China [111].

2.1.2 Human/Animal-Based Treatment

Human or animal-derived remedies are significantly based upon the production of hormones, antibodies, secretion to the treatment of diseases. Plasma treatment is an example of specifically used remedies in the critical stage of COVID-19 treatment.

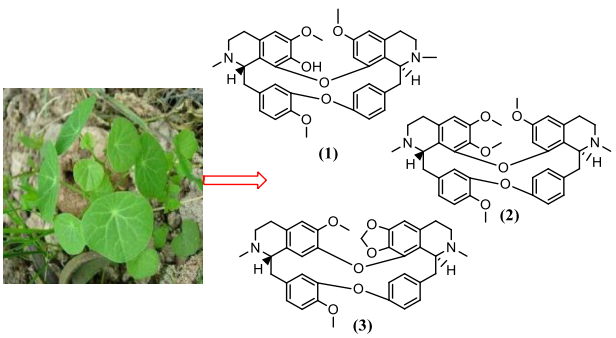


Fig. 2 Stephania plants extracted drugs for COVID-19 in human

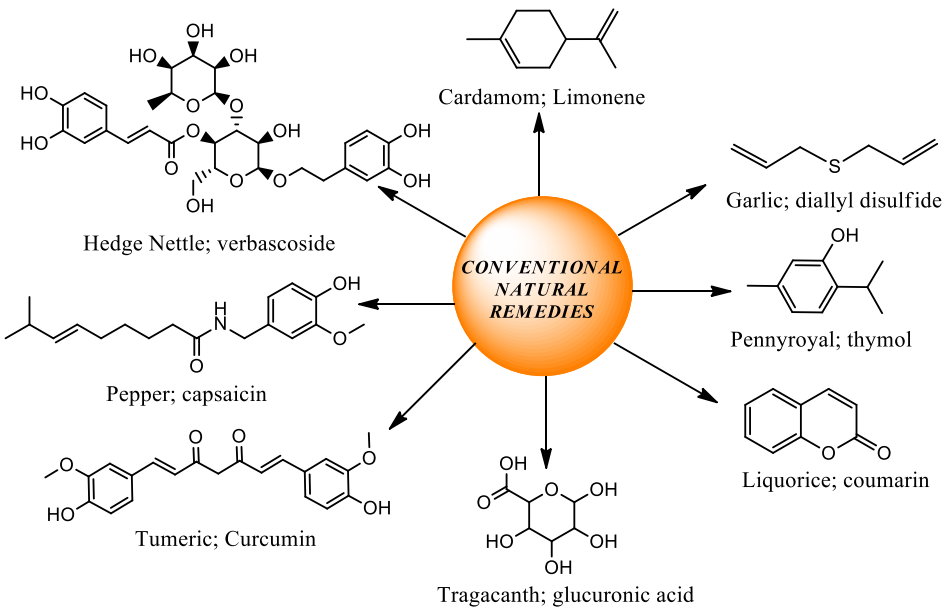


Fig. 3 Asian conventional natural remedies

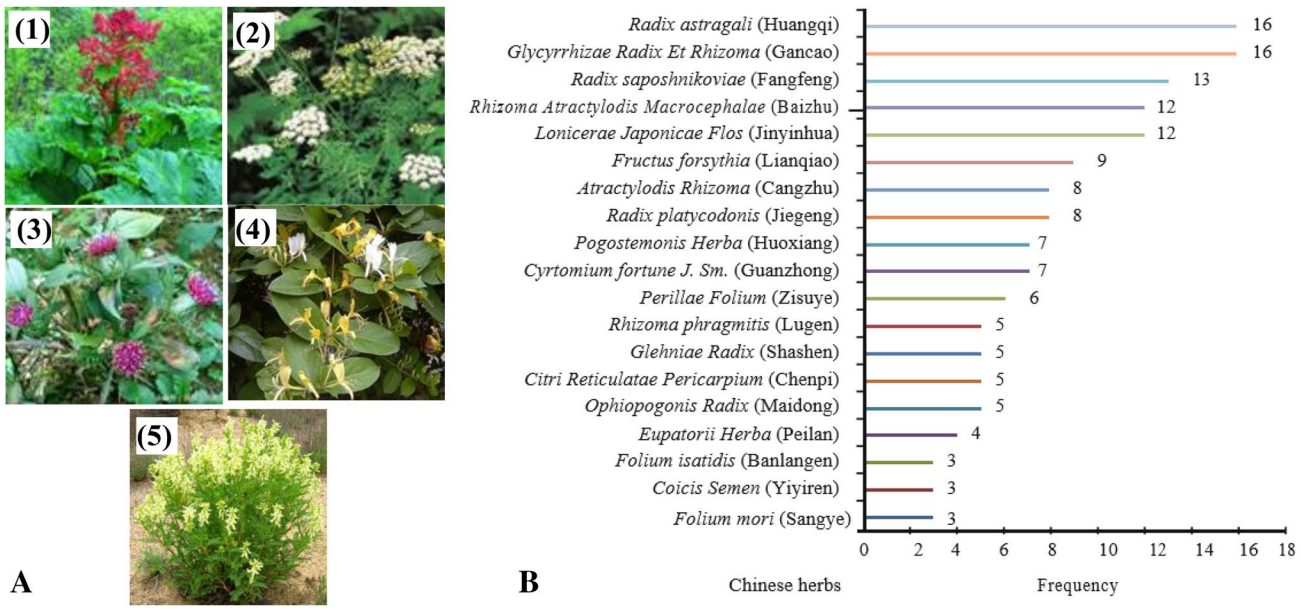


Fig. 4 Chinese natural herbs as antiviral (**a**) and frequency of natural herbs for COVID-19 (**b**)

2.1.2.1 Plasma Treatment Utilizing plasma from human blood who has recuperated from illness has been an alternative method to cure COVID-19. Plasma contains a natural antibody [112] which is helpful for the critical stage treatment known as plasma treatment of passive antibody therapy (Fig. 5) [113]. Human 'sera' of convalescent patients (coronavirus disease recovered patients) cross neutralized SARS-CoV-2 S-driven entry [114, 115]. Convalescent plasma has successfully contributed to the COVID-19 recovery after the transfusion of plasma to bring the patient to the normal body temperature [116]. Plasma exchange therapy is an old treatment but found it helpful to fight for fatal COVID-19 [117]. Serological tests were recorded for confirmation of the efficiency of antibodies for coronavirus disease treatment via neutralization before the usage of plasma [118, 119].

The spike protein is responsible for the formation of severe respiratory infection through the coronavirus by fusion or correlating with cellular receptors to target cells [120]. The ACE2 (angiotensin-converting enzyme

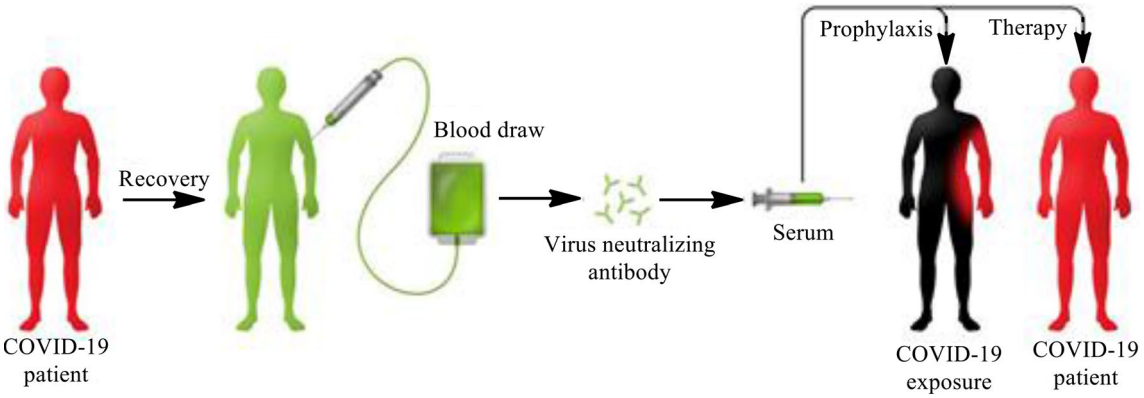


Fig. 5 Passive antibody therapy or plasma treatment for COVID-19 © American Society for Clinical Investigation

2) is a carboxypeptidase, which effectively terminates angiotensin II to angiotensin, has been recognized as a potent receptor for coronavirus. The recombinant protein achieved by the fusion of human extracellular domain ACE2 with the Fc section of human immunoglobulin IgG1 designated as ACE2-Ig contributed to the neutralization of spike protein [112]. The spike has a strong binding affinity with the receptor-binding domain (RBD) of coronaviruses and employs anticipated therapeutically properties [121]. In critical situations, plasma therapy is highly potential, more effective, easy to handle and safe for quick recovery of patients [122, 123].

2.1.3 Microorganisms-Based Treatment

Microorganisms such as algae, fungi and bacteria have also contained bioactive compounds and used to treat coronavirus [124]. Metabolites from fungal contained reactive moieties for protease inhibitors against SARS-CoV-2. Taxol or paclitaxel are examples of active metabolites extracted from fungal species i.e. *Pestlotia*, *Pithomyces* and have been reported for coronavirus treatments due to anti-HIV activity [125]. Patel and his coworkers have explored the fungal metabolites i.e. quercitrin (*G. triplex*), bergenin (*D. indusiata*) and dihydroartemisinin (*C. stercoreus*) through computational studies, which shows potential remedies to inhibit the main protease of SARS-CoV-2 [126].

Marine organisms are a well-known source for drug discovery in the therapeutic field [127]. Brown algae species such as *Sargassum spinuligerum* and *Ecklonia cava* has potential remedies against major protease protein of SARS-CoV-2 due to the presence of bioactive compounds 1,3,5-trihydroxybenzene and 8,8′-Bieckol, Dieckol, 6,6′-Bieckol [128, 129]. Moreover, microorganisms derived β-glucans can immune the body against coronavirus infections [130].

2.2 Synthetic Remedies

Western-style methods to cure any disease is recognized as allopathic treatment [131]. In cases of pneumonia and positive coronavirus test, antiviral drugs are recommended to the patients, but in emergency cases, supplementary oxygen is highly suggested [132–134]. Due to quick spreading of COVID-19 crisis, previously reported antiviral, antimalarial or antiparasitic drugs (i.e. riboflavin [135], lopinavir [136], oseltamivir [137], lopinavir/ritonavir [138], minocycline [139], tocilizumab [140], ribavirin [141, 142], niclosamide [143], corticosteroids [144], and ciclesonide [145]) have been utilized for treatment. The clinical and laboratory trials are challenging to modern medicines [146–148] that is still under investigation. The promising outcomes of few drugs are illustrated below:

2.2.1 Ivermectin

Ivermectin is a recognized Food and Drug Administration (FDA) approved antiparasitic drug [149] with potent antiviral activities [150]. Ivermectin, which previously reported to possess in vitro antiviral activity against a broad spectrum of coronaviruses [151, 152] has been recently reported as a potent inhibitor of SARS-CoV-2 infections with excellent ability to suppress pathogenic virus against in vero-hSLAM cells model. Caly et al. have recently reported on the effect of ivermectin on infected cells compared to the vehicle DMSO. Effective suppression of all viral materials after 48 h was demonstrated by the reduction in cell-associated viral RNA with an increase to an ~ 5000-fold in ivermectin-treated compared to control samples. The samples were prepared by using viral load through real-time PCR, then IC_{50} values were achieved using GraphPad prism after 48 h on cell-associated virus and supernatant against COVID-19 E-gene and RdRp gene by treating with different concentration of

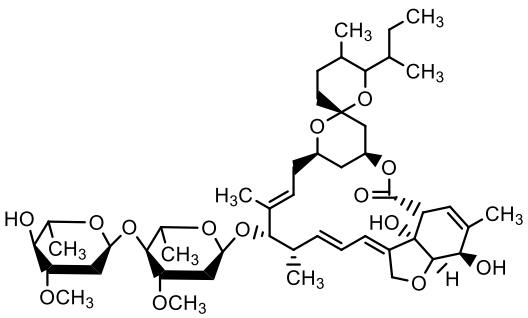


Fig. 6 FDA approved drug ivermectin

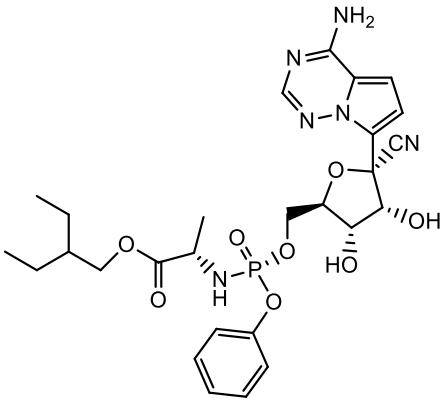


Fig. 7 Chemical structure of remdesivir

ivermectin. IC_{50} depicted ivermectin is potentially efficient against the inhibition of viral infection (Fig. 6) [153].

2.2.2 Remdesivir

Remdesivir (RDV) is another potential antiviral drug [154, 155] used to de-accelerate the RNA viral infections of SARS-CoV-2 (Fig. 7) [156]. It was reported by Holshue et al. on the successful recovery of COVID-19 patients by using remdesivir. Nevertheless, treating severe coronavirus patients with remdesivir [157] has not shown good responses. A comparative analysis of various drugs i.e. remdesivir, ribavirin [158], nitazoxanide, pencilovir, favipiravir, chloroquine and nafamostat has been comprehensively studied against COVID-19. The Vero E6 cells were infected with SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05 and different concentrations of antiviral drugs for 48 h. The half-maximal effective concentration (EC_{50}) values and cytotoxicity percentage were evaluated by qRT-PCR and CCK-8 assays, respectively, which depicted all drugs have good inhibition activities. Interestingly, the low-micromolar concentration or less dosage of remdesivir is more effective to cure fatal corona disease [159]. There are instances that

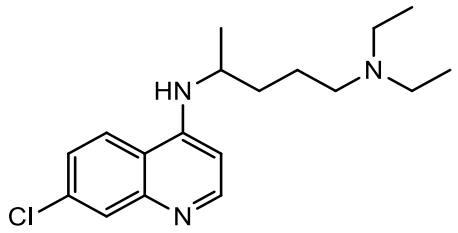


Fig. 8 Chemical structure of chloroquine

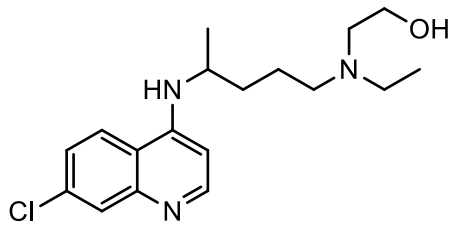


Fig. 9 Structure of hydroxychloroquine

excess dosage could damage human organs especially on lung tissue [160].

2.2.3 Chloroquine

Chloroquine is another well-known autoimmune and antimalarial drug [161]. Chloroquine (Fig. 8) is a recognized drug to stop viral infection by enhancing the endosomal pH essential for the virus [162], besides intrusive the glycosylation of coronavirus cellular receptors [163]. The addition of chloroquine in the infected sample exhibited antiviral activity against COVID-19. Chloroquine has an immune-controlling activity, which interactively boosts up the in vivo antiviral effect. The drug is extensively reactive and distributed quickly to the whole body [159]. Essentially, the significance of chloroquine therapy is based upon age, stage of the disease and medicinal performance [164].

2.2.4 Hydroxychloroquine

Hydroxychloroquine (HCQ) (Fig. 9) [165] is a derivative of chloroquine and recently gazette as an authorized medicine for the treatment of corona disease [166]. A comparison of the properties of chloroquine and HCQ is depicted in Table 1 [163, 167, 168]. The severity of both HCQ and chloroquine can be reduced via assimilation with zinc supplement as zinc substance has been reported with a capability to reduce SARS-CoV-2 infection [169].

A recent study has been reported on the effective dosage of HCQ that can inhibit viral infection detected via WebPlotDigitizer (v4.2) software based on EC_{50}. The observed

Table 1 Chloroquine and hydroxychloroquine comparison for COVID-19

Properties	Chloroquine	Hydroxychloroquine
Family	Aminoquinolines	Aminoquinolines
Availability	Not common/limited	Common
Toxic	More	Less
Nature	Hazardous	Safe
Solubility	Less	More
Oral toxicity	More	Less
Functioning	inhibit viral infection	inhibit viral infection

EC_{50} was 4.7 μM, which is comparable to the in vitro EC_{50}'s. The tremendous decrease in viral effect has been reported with HCQ doses > 400 mg twice in 1 day for ≥ 5 days against SARS-CoV-2 compared to the lower routine dose (≤ 400 mg daily). However, the HCQ > 600 mg dosage twice in 1 day was also effective. In contrast, the lower HCQ dose treatments may be insignificant to respond against the virus [170, 171].

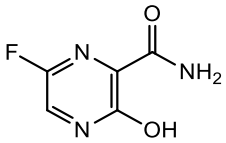
Incorporation of HCQ with azithromycin has produced synergistic repletion in viral infection as the azithromycin drugs able to increase the efficacy of the drugs [172]. Both drugs are cheap and commercially available [173]. Gautret et al. [174] have also reported on the efficiency of azithromycin incorporated with hydroxychloroquine and hydroxychloroquine for the treatment of COVID-19.

Hydroxychloroquine has recently become a controversial drug due to its discouraging results. WHO has suggestedbanning hydroxychloroquine to be used for COVID-19 treatment [175] due to the adverse effects on retina tissues, cardiac muscles, central nervous system and cause genotoxicity in DNA and liver cells [176]. Initial clinical results confirmed this drug has been found anti-SARS-CoV-2 effects both in vivo and in vitro and may have an effect on the treatment of coronavirus disease [177]. These unreliable experiences have also highlighted the misleading nature of controlled experimental trials.

2.2.5 Favipiravir/Favilavir

Favipiravir or favilavir is an excellent antiviral [178] drug, traditionally known as Avigan and manufactured by Fujifilm [179] Toyama Chemical Company in Japan and China. Favipiravir has also been applied for coronavirus patients with improbability remains about drug effectiveness and safety [180]. However, this antiviral drug cause minor side effects [181]. The Favipiravir drug (Fig. 10) can be expressively inhibited viral clearance with a higher chest CT scan and depicted better improvement rates in moderate COVID-19 patients as compared to Lopinavir/Ritonavir [182].

Fig. 10 General structure of favipiravir



3 Advantages and Limitations of Natural and Synthetic Drugs

In summary, natural remedies are beneficial due to strong binding affinity, high efficacy and less side effects; whereas synthetic remedies are very reactive but indirectly may cause damage to other tissues or organs in the human body. Despite several advantages have been reported on natural and synthetic remedies, the effectiveness of both remedies is mainly depending upon the condition of patients (i.e. mild, moderate, severe, critical) and the selection of medicinal protocol. The excessive dosage of synthetic remedies, however, is very hazardous as compared to natural remedies. Natural remedies gave more advantages and safer with limited drawbacks.

4 Conclusion

In searching for potential remedies of antiviral drugs, the production and discovery of antiviral agents from natural and synthetic sources have been intensively developed. The outcomes of these studies indicated that drugs derived from natural resources as bioactive antiviral compounds have more potential to cure coronavirus infection as compared to synthetic drugs with less side effects. Currently, clinical tests still ongoing on the suitable and effective medical treatment of COVID-19, which authentically supports the recovery chances of patient and toxicity of the drug, the effectiveness of drug synthesis to inhibit viral infection and the replication process. This review is particularly significant in the drug discovery process and exclusively describes the potential treatments by utilizing natural and synthetic drugs against coronavirus disease. The benefit and aftereffects of both remedies have led scientists to search for more appropriate potential remedies against coronavirus ailments.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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