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COVID-19 a global crisis: Features, complications and suggested treatments

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Abstract

Coronavirus disease 2019 (COVID-19); caused by the novel coronavirus (SARS-CoV-2) is the talk of everyone all over the world in 2020 since it has been considered as a public health emergency of international concern by WHO in 30th January, 2020. COVID-19 is a highly transmittable disease with different symptoms which can vary from mild to severe and life threatening. Scientists all over the world are working on finding a treatment or vaccine for this disease. All of these studies are currently not finished yet during writing this review. However, in this review a summary about the current status of these studies is given. This summary includes medicinal plants and natural products, antivirals like remdesivir, favipiravir, oseltamivir and nelfinavir as well as other miscellaneous drugs like chloroquine, hydroxychloroquine and ivermectin which showed promising results in treating COVID-19. In conclusion, the review recommends conducting further investigations worldwide and reporting them in peer-reviewed publications to aid in improving the drugs' dosing regimens and clinical studies.

Keywords: Covid-19; SARS-CoV-2; Pneumonia; Vaccination; Antivirals; Hydroxychloroquine

Introduction

Coronaviruses are large group of viruses which were not highly pathogenic to humans till the occurrence of the first outbreak of the severe acute respiratory syndrome (SARS) in Novemebr, 2002 in Guangdong, China [1]. In 2012, the second outbreak of the Middle East respiratory syndrome (MERS) emerged by another new coronavirus in Saudi Arabia [2]. Both epidemics highlighted the great threat which these types of viruses could make globally to the health security [3]. Finally in December, 2019 in Wuhan, China the third coronavirus epidemic originated. As discovered at the end of 2019, it was called by World Health Organization (WHO) on 12th January, 2020 as COVID-19 [4]. COVID-19 was declared a global pandemic by the WHO on 11th March, 2020 [5]. The International Committee on Taxonomy of Viruses (ICTV) named the causing virus of COVID-19 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6].

Coronaviruses are characterized by the presence of crown-like spikes on their surfaces. Many coronaviruses can circulate and transmit between animals however some of them can infect humans (7 types). Occurrence of SARS, MERS and COVID-19 might be associated with civet cats, camels and bats, respectively [7]. Unfortunately, 213 countries around the world have recorded 5,103,350 infected cases and a total of 329,925 deaths from COVID-19 [8]. This confirmed the severity of the disease compared to SARS (from 1 November 2002 to 31 July 2003) and MERS (since 2012) where the number of deaths were 774 [9] and 858, in that order [10].

A comparison between the three diseases caused by coronaviruses is collected in Table 1.

The number of scientific papers recorded in PubMed in 2020 using a search term "Treatment of COVD-19" was 1696. Additionally, searching using "COVID-19 articles" and "COVID-19 reviews" resulted in 3840 and 704 records, in that order. These statistical results in one year represent the very great importance of the topic and the need for further investigations to combat the virus and win the battle. Hence, the authors are presenting this review to highlight on the possible ways of prevention and treatment of COVID-19 as well as offering new suggestions to pass the crisis.

Table 1: Brief comparison between SARS, MERS, and COVID-19 diseases

Comparison points \ Disease	SARS	MERS	COVID-19
Causing virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Year of the outbreak	2002	2012	2019
Country of origin	China	Saudi Arabia	China
Disease spread	Epidemic	Epidemic	Pandemic
Key hosts	Civet cats	Camels	Bats
Number of deaths	774 (1 November 2002 to 31 July 2003)	885 (since 2012)	329,925 (On 21st May)
Year of containment	2003	Not identified	Not yet

Methods of transmission

Unfortunately, all the countries all over the world weren't prepared for such highly infectious and transmitting disease, creating an exceptional stress on all healthcare systems. The transmission rate of SARS-CoV-2 is higher than any other corona viruses which might be due to the genetic mutations [11]. Person to person transmittance is the major method of infection. Additionally, transmission through fomites has been reported [12]. This way of transmittance is called cross-contamination which may occur from contaminated surfaces–by other people or even yourself- which can be a possible way of transmitting the disease if the person touched these surfaces then put his hands on eyes, nose or mouth. Although, using a mask or gloves can keep us safe however touching them with dirty hands can be a source of infection [13]. So, the best advice to protect ourselves form infection is hand-washing using soap and water [13]. Additionally, proactive detection for the confirmed cases is of great importance for isolation measures.

Regarding the air-borne transmittance, it is still controversial. A study conducted by Su et al, negated the possibility of air-borne transmittance of the virus after analyzing air samples in the environment of symptomatic COVID-19 patients [12, 14]. However, the WHO didn't give a final decision about this issue till more studies are conducted and published.

Transmission and spread can also occur through conjunctiva [15]. Special attention should be given also to closed areas where non-fresh air can lead to increased virus density causing facile spread. Hence, developing an effective anti-viral drug to eradicate or even reduce the viral load is required promptly to limit the progression of the disease and to stop its transmission.

Symptoms

Disease symptoms may happen within 2 to 14 days after being exposed to the virus. SARS-CoV-2 can infect any age range, however geriatrics, adults with chronic diseases like diabetes, heart or lung diseases and pregnant women are more vulnerable to more severe complications from COVID-19 [16, 17]. Several studies stated that men are more affected by SARS-CoV-2 than women [18, 19], however this gender difference might be due to different exposure due to work needs reporting and susceptibility.

COVID-19 occurs more frequently among adults more than or equal to 15 years old, with little proportion of infections among children. Unfortunately, this hypothesis didn't offer special preventive measures for children -like wearing masks- which resulted in increasing the number of infected children [20]. Consequently, the PCR stated that children are vulnerable to COVID-19 disease due to their immature immune system [21]. Hence, more attention should be given to these age range (among infants and children) especially that they are not mature enough to protect themselves or even describe their medical situation as well as they more susceptible to cross contamination from their families. Literature includes several examples for symptomatic and asymptomatic children with COVID-19 [21-23].

Symptoms range from mild to severe. Mild symptoms are like having cough, sore throat, fever, chills, muscle pain, headache and short breath, while severe ones include chest pain, persistent high fever, pneumonia and difficulty to breath requiring prompt hospitalization and mechanical ventilation [17]. A comparison between common cold and COVID-19 symptoms is collected briefly [24] in Table 2.

Economic impact of COVID-19

The continuously and rapidly increasing numbers of confirmed cases and deaths are posing extreme challenges on all the countries, which require a worldwide solidarity strategy [25]. The worldwide map of the spread of COVID-19 is presented in Figure 1 [26]. Almost all the affected countries are imposing strict precautionary measures like lockdown and airlines lock which in turn has negative economic impacts causing challenging economic crises. Although the problem is worldwide however its economic effect is deeply local. Investment in public health would assist in the rapid recovery from COVID-19 pandemic. The World Bank Group launched emergency health support to help developing countries to combat COVID-19 providing $160 billion over the next 15 months [27].

Table 2: A brief comparison between common cold and COVID-19 symptoms

Symptoms / Disease	Common cold	COVID-19
Cough	Sometimes	Persistent and dry
Fever	Sometimes	Present and can be of high grade
Runny nose	Present	Sometimes
Sneezing	Present	Sometimes
Fatigue	Present	Ranges from mild to severe
Conjunctivitis	Sometimes	Present and can be very severe
Relief by anti-histaminics	Yes	No
Difficulty in breathing	No	Yes and sometimes is very severe
Need for mechanical ventilation	No	Sometimes

Hence, this review introduces the different trials conducted for developing a safe and effective vaccine as well as an efficient medication. An illustrative figure combining the symptoms and different effects of COVID-19 as well as the required measures are presented in Figure 2.

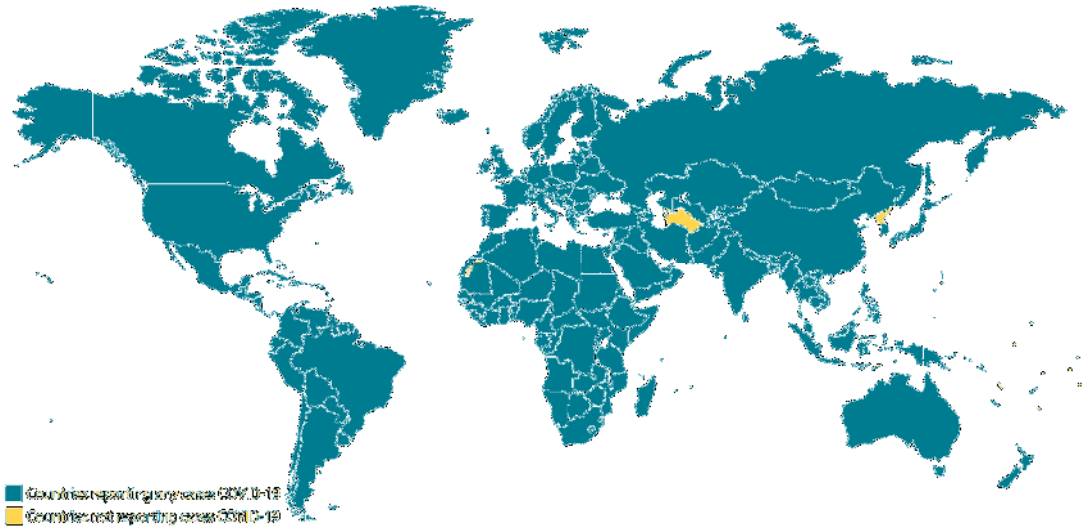

Fig. 1: Global map of confirmed cases of COVID-19 *(accessed on 21st May 2020)*

Vaccination

No vaccine is available up till now for COVID-19 disease, however there are several attempts for developing such vaccine. The WHO started an initiative called "WHO Solidarity Trial" for hastening the development of an effective vaccine against COVID-19 [28]. WHO stated in February, 2020 that it is not expected to get a vaccine against SARS-CoV-2 before 18 months. On the other hand, the Coalition for Epidemic Preparedness Innovations (CEPI) indicated in April, 2020 that a vaccine may be available under emergency use by early 2021. On 8th April, 2020, 115 vaccine candidates were in development, with five organizations having initiated phase 1 safety studies in human subjects [29]. CEPI increased the funding for phase 1 and 2 clinical trials on Novavax 'NVX-CoV2373' vaccine as well as supporting its large scale production. Phase 1 results are expected to be ready in July, 2020 [30]. On 5th May, CEPI has launched a call for funding to accelerate the global COVID-19 vaccine development guided by three imperatives: speed of manufacture, safety and global accessiblity [31].

On 16th March, 2020, Jennifer Haller a 43 old American citizen and three more participants were the first to be enrolled in phase 1 clinical trials at the Kaiser Permanente Washington Health Research Institute in Seattle on mRNA-1273 vaccine developed by the National Institutes of Health and is made from synthetic virus particles depending on digital information instead of using physical virus. All participants will be monitored for 14 months to

decide the efficacy of the vaccine, however up till now no side effects were recorded [32].
International cooperation between all vaccine developers, funders, health sectors and countries is required to support the prompt production of an effective vaccine in sufficient amounts and to ensure supplying all countries especially low-resources ones.

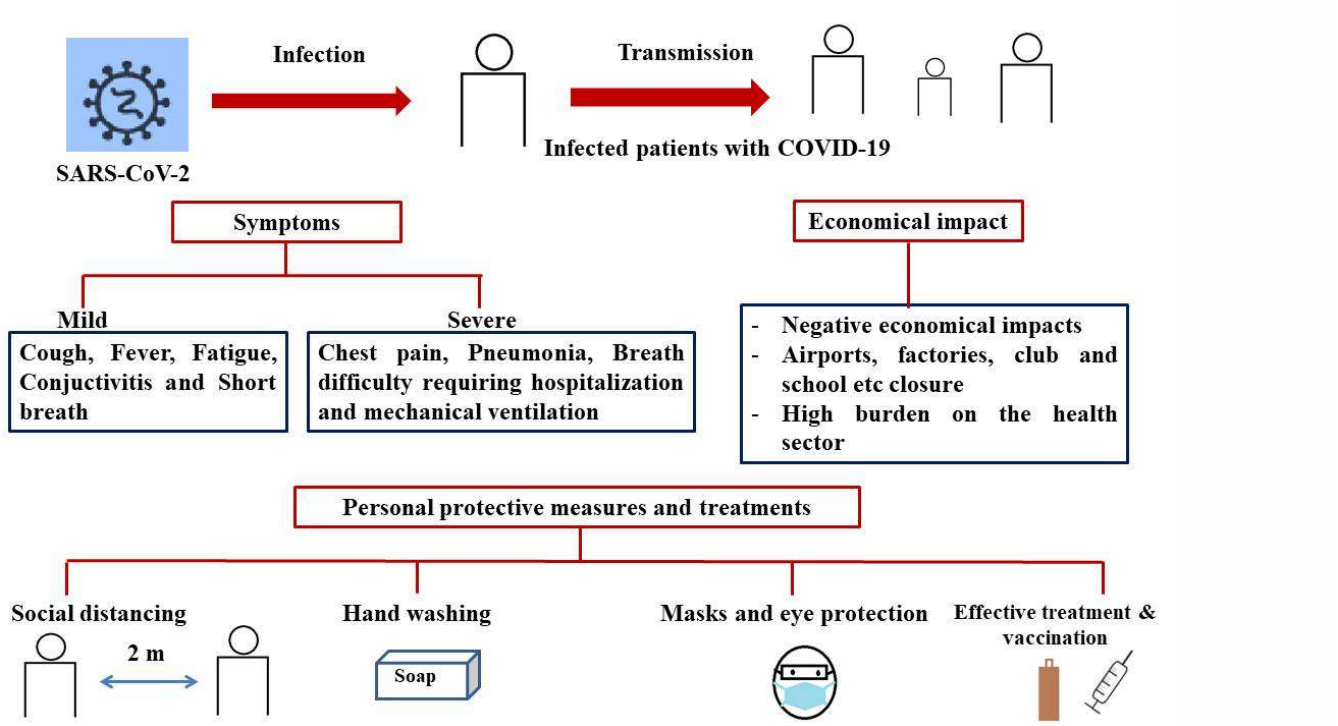

Fig. 2: An illustrative diagram representing the transmission, symptoms, different effects of COVID-19 as well as the required measures.

Prevention and treatments

Medicinal Plants and natural products

Several medicinal plants and their extracted compounds have been reported to have antiviral activities against several viral infections such as those caused by coronavirus [33-36]. Cinatl et al. assessed the antiviral activity of several medicinal compounds in Vero cells against 2 clinical coronavirus isolates (FFM-1 and FFM-2) from SARS infected patients. Of all the tested compounds, glycyrrhizin extracted from liquorice roots showed to be the most active in preventing the replication of the SARS virus. They suggested that glycyrrhizin should be evaluated for treating SARS [37]. Another study conducted by Wen and coworkers stated that 221 phytocompounds were evaluated for their activity against SARS-CoV. They used a cell-based assay measuring SARS-CoV-induced cytopathogenic effects on Vero E6 cells. They observed that about 20 out of the 221 phytocompounds especially; pecific abietane-type diterpenoids and lignoids were potent inhibitors for SARS-CoV [38]. Moreover, Khaerunnisa et al., assessed some bioactive compounds found in several medicinal plants as potential COVID-19 main protease inhibitors, using a molecular docking study. They found that kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin- gallate might act as COVID-19 main protease inhibitors; however further investigations are required to approve their medicinal benefits [39].

Vitamin D is a fat soluble pro-hormone that supports the immune system [40]. Unfortunately, not much food is rich in vitamin D. Vitamin D3 is formed in skin after exposure to ultraviolet B rays from sunlight which is further activated by liver and kidney [41]. However, this process decreases by aging and during winter season; subjecting elderly people and citizens of cold countries especially at latitudes more than 40° to vitamin D deficiency problems [42]. This seasonal deficiency has been associated with respiratory infections like the spread of influenza virus in winter [43-45]. Vitamin D is essential for regulating and suppressing the inflammatory cytokine response hence avoiding the incidence of acute respiratory distress syndrome [46-48]. The failure of this inflammatory cytokine response suppression was indicated to be responsible for the severe complications of COVID-19 [49]. Additionally, the geographical correlation between vitamin D deficiency and the elevated infection and mortality rates due to COVID-19 could support the beneficial effect of vitamin D on COVID-19 patients. It was previously stated by Daneshkhah et al that the rate of fatality from COVID-19 was very high in Italy, Spain, France and European countries with high incidence of vitamin D deficiency [50]. Additionally, Rhodes et al. showed that the mortality rate from COVID-19 was

moderately low for territories below 35° latitude [51]. Hence, supplementation with vitamin D might help in reducing the mortality rates from the pandemic. This suggestion was published before by Marik et al [52].
Based on these preliminary promising results, this review highlights the need to exploit the medicinal plants as well as natural products in treating COVID-19 infected patients to benefit from their low costs and availability, more and above being natural is highly appreciated.

Antiviral drugs

Several antiviral drugs are currently under investigation for their efficacy against COVID-19. They exert their activity by different actions such as protease inhibition, neuraminidase inhibition and as being nucleoside analogs [53]. These antiviral drugs are used in clinical trials either alone or with multiple combinations with other drugs such as interferon, hydroxychloroquine and azithromycin [54]. This review focuses here on the most promising candidates in treatment of COVID-19.

Remdesivir

Remdesivir (formerly known as GS-5734) is a nucleotide analogue inhibitor of viral RNA-dependent RNA-polymerase [55]. It is the most promising direct-acting antiviral currently being investigated for COVID-19. It is not currently approved for any indication. In 2nd April 2020, its compassionate use was accepted by the European medicines agency Committee for Medicinal Products for Human Use (CHMP) [56]. In 1st May 2020, U.S. Food and drug administration has approved emergency use authorization for remdesivir in treating hospitalized COVID-19 patients [57]. This will increase and facilitate its use in different hospitals but with strict regulations and in severe cases. Remdesivir for compassionate use is provided in two dosage forms, “concentrate for solution for infusion” and “powder for concentrate for solution for infusion” [56].
Remdesivir is a prodrug which is converted after intravenous administration into an intermediate metabolite (GS-704277) as well as a nucleoside one (GS-441524). Then inside the cells, the GS-441524 monophosphate is converted rapidly into the pharmacologically active analog of adenosine triphosphate (GS-443902) which inhibits viral RNA polymerases. It is not suitable for oral administration as it will be subjected to extensive first pass metabolism [58]. As being still under investigation, its safety profile is incompletely characterized. The solitary side effect that seems clearly linked to the use of remdesivir is increasing the transaminases. But generally regarding its use in COVID-19, the safety profile is compatible with compassionate use in the proposed target population [56].
There are several clinical trials which began in US, China and other countries to test the efficacy of remdesivir in COVID-19 patients. In the study performed in China by Wang et al on adult hospitalized patients for severe COVID-19, patients were randomized in a ratio of 2:1 to take remdesivir (200 mg IV on day 1, then 100 mg IV once daily from 2nd to 10th day) or placebo; started within 12 days of symptoms onset. Intention to treat (ITT) population included 158 patients treated with remdesivir and 78 patients treated with placebo; some of the treated patients received interferon α-2b or lopinavir–ritonavir or corticosteroids during hospitalization. They concluded that remdesivir didn’t show any statistically significant clinical benefits. Nevertheless, the obtained numerical reduction in time till clinical progress in patients treated before needs to be confirmed in larger studies. Registration was ended before the pre-specified number of patients was reached as the outbreak of COVID-19 was controlled in China [59]. In a different study sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) with ClinicalTrials.gov, patients received remdesivir (200 mg IV on day 1, then 100 mg once daily during the hospitalization period of up to 10 days total) or placebo [60]. Preliminary data analysis indicated smaller median time to recover in remdesivir group (11 days) *versus* placebo group (15 days) and recommended that remdesivir treatment might have delivered a survival benefit (mortality rate 8% in remdesivir group *versus* 11.6% in placebo group [61]. The remdesivir manufacturer (Gilead company) is studying extensively the safety as well as the antiviral activity of remdesivir in contributors with severe COVID-19 complications [60]. Gilead conducted a study to investigate if a shorter period (5 days) of treatment would give the same clinical efficacy as longer period of 10 days. Gilead proclaimed that the available information for the first 397 participants with pneumonia and reduced levels of oxygen but not requiring mechanical ventilation indicated comparable clinical enhancement with both treatment durations. The duration to clinical improvement in half the participants in the 5-day treatment group was 10 days *versus* 11 days in the 10-day treatment group. Clinical recovery after 14 days was achieved in 64.5% and 53.8% of the patients in the short and long duration treatment groups, correspondingly. Generally, it was concluded that early treatment would assist in improving clinical outcomes as participants who were treated within 10 days of symptom onset possessed enhanced clinical outcomes in comparison to other patients who took medication after 10 days of symptoms [62]. Another study carried out by Gilead is appraising the safety and antiviral activity of remdesivir after 5 and 10 days of treatment but in conjunction with standard of care in comparison to the standard of care alone [60]. The results from the first 600 patients of this study are expected at the end of May [62].

Favipiravir

Favipiravir is another antiviral drug under investigation for treatment of COVID-19. It was approved for treatment of influenza in 2014 in Japan. But this approval was limited to certain cases; just when the government judges that the drug can be used as a countermeasure against new or re-emerging influenza viruses [63]. Moreover, favipiravir has been used for further indications for severe fever with thrombocytopenia syndrome depending on clinical trials besides influenza in Japan [64]. Favipiravir is available as film coated tablets under the trade name of Avigan tablets. Favipiravir is a prodrug which is metabolized into the active form; favipiravir ribosyl triphosphate by an intracellular

enzyme. This active form selectively inhibits viral RNA-dependent RNA polymerase, preventing replication of the virus [65]. Favipiravir is rapidly absorbed after oral administration with high bioavailability near to 100%. It is mainly eliminated through hepatic metabolism by aldehyde oxidase, and marginally xanthine oxidase, giving inactive metabolite, which is removed in the urine [66]. Adverse effects of favipiravir are still not accurately stated, as Avigan hasn't been administered with the approved dosage before the COVID-19 pandemic. In Japanese clinical studies and the global phase 3 study performed on lower therapeutic doses, chief opposing reactions comprised rise in blood uric acid level in 24 participants (4.79%), diarrhea in 24 participants (4.79%), decrease of neutrophil count in 9 participants (1.80%), increase of AST enzymes in 9 participants (1.80%), increase of ALT enzymes in 8 participants (1.60%) [63].

Safety and efficacy of the drug is now under investigation in multiple clinical trials in patients with COVID-19 in China, Japan and other countries. Wang et al carried out an open-label multicenter trial on adult infected patients with COVID-19. Patients were randomly classified in a 1:1 ratio to get the conventional therapy in addition to favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 10 days) or umifenovir (200 mg 3 times daily for 10 days). Both groups were judged according the clinical recovery rate on the seventh day where results clarified that no significant difference was detected between both groups. On the other hand, favipiravir significantly shortened the latency for pyrexia and cough relief. Moreover, they concluded that antiviral-related opposing effects of favipiravir are mild and controllable [67].

In another small, open-label, non-randomized study in COVID-19 patients in China conducted by Liu et al, favipiravir (n=35) was compared *versus* lopinavir/ritonavir (n=45). Favipiravir was administered in a dose regimen as follows: 1600 mg orally twice daily on the first day followed by 600 mg orally twice daily on days 2 to 14 while lopinavir/ritonavir were administered twice daily (400 mg/100 mg) from days 1 to 14. In addition, the two groups received aerosolized interferon α-1b. In comparison to lopinavir/ritonavir group, it was observed that favipiravir group was accompanied with reduced median time to viral clearance (4 *versus* 11 days) and advanced improvement rate on chest CT imaging on day 14 (91 *versus* 62%). Based on their findings, they concluded that favipiravir showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance [68]. This study could provide significant information for establishing standard treatment guidelines for treating COVID-19.

Oseltamivir

Oseltamivir is a viral neuraminidase inhibitor. It is approved by FDA under trade name, Tamiflu for treating influenza virus [55]. Oseltamivir is available in two dosage forms; capsules and powder for oral suspension [69].

Oseltamivir is marketed in the form of phosphate salt which is a prodrug. After oral administration, it is rapidly converted by hepatic esterases into the active carboxylate form which has an absolute bioavailability of about 80%. It is systemically distributed reaching the lung in therapeutic concentrations [70]. Oseltamivir has a broad safety margin in acute, subacute and chronic toxicity studies [71]. Moreover, it is well tolerated with mild side effects like nausea and vomiting. On the other hand, rare serious skin hypersensitivity reactions and neuropsychiatric events have been reported in post marketing experience [69].

Oseltamivir use for COVID-19 has been reported in China with and without either corticosteroids or antibiotics. But there is no precise indication to date that oseltamivir is efficient in the treatment of COVID-19 [54]. In 9th May 2020, 17 clinical trials for COVID-19 that included the use of oseltamivir were available at Clinicaltrials.gov [60]. It is used in these clinical trials with multiple combinations with different drugs such as hydroxychloroquine, azithromycin, lopinavir/ritonavir, and favipiravir. None of these studies has been completed till this day.

Nelfinavir mesylate

Nelfinavir is an HIV-1 protease inhibitor [72]. It has low and variable bioavailability [73]. The bioavailability of the drug differs according to the age where infants (1 year old) require higher doses in comparison to older children and adults which might be attributed to the extensive first pass metabolism or feeding protocols in infants [74].

Nelfinavir has shown strong inhibition against SARS-CoV. Nelfinavir acted by inhibiting the cytopathic effect induced by the virus as well as reducing the production of virions from Vero cells. It was also observed that the expression of the viral antigens decreased in treated cells with nelfinavir in comparison to untreated ones. This study suggested the use of nelfinavir in extra clinical studies as an anti-SARS drug [72]. Hence, nelfinavir could be a good lead for designing an effective treatment against COVID-19. Nelfinavir showed certain activity against SARS-CoV-2 replication [75]. Transient transfection of African green monkey kidney (Vero) cells with SARS-CoV-2 resulted in extensive cell fusion mainly due to expression of SARS CoV-2 S (S-n) glycoprotein and to some extent due to SARS S (S-o) glycoprotein. S-n glycoprotein is responsible for formation of large multinucleated cells 48 h after transfection. Nelfinavir (10 □M) succeeded to inhibit S-n and S-o cell fusion mechanisms. Additionally, nelfinavir might inhibit S proteolytic processing [76]. These results open the door for extra applications of the drug for treating COVID-19 patients especially at early stages of the disease.

Some Japanese researchers stated that combining nelfinavir and cepharanthine (anti-inflammatory) showed effective clearing of SARS-CoV-2 virus in laboratory investigations. Nelfinavir inhibits the virus replication by binding it while cepharanthine halts the attachment and entering of the virus to the cells [77].

Miscellaneous drugs

Chloroquine phosphate

Chloroquine phosphate is the effective synthetic substitute of natural quinine [78, 79]. For several decades, chloroquine was prescribed as the first choice for the prophylaxis and treatment of malaria [80]. Chloroquine has high oral bioavailability approaching 78 and 89 % for solutions and tablets, in that order. Tissue bio-distribution indicated high accumulations of the drug in several tissues like liver and lungs. However, the drug has a narrow therapeutic range, which could result in drug poisoning effects; e.g, cardiovascular disorders [81].

Besides its use as an antimalarial drug, chloroquine is also effective in treating some types of autoimmune diseases [82]. Additionally, this drug showed good antibacterial, antifungal as well as antiviral activity [83]. This antiviral effect represented in its ability to inhibit the virus replication cycle was more explored after repositioning the drug in the treatment of human immunodeficiency virus in the middle of the 90s, although not highly effective [84]. This repositioning and repurposing of the drug was mainly attributed to its low cost and tolerability [85]. Evidences for some antiviral activity has been found in mice against some viruses like human coronavirus OC43 [86], enterovirus EV-A71 [87] and influenza A H5N1 [88]. However, it was not effective against influenza virus in ferrets [89] as well as in clinical trials [90]. A promising effect against hepatitis C was observed in pilot study in non-responder patients, where a transient reduction in virus load was detected [91].

With respect to coronaviruses, chloroquine showed notably the good therapeutic benefits against SARS-CoV-1 [85, 86]. Additionally, it was reported by Keyaerts et al., that the growth of SARS coronavirus could be inhibited in cell cultures by chloroquine and hydroxychloroquine [92].

It was detected that SARS-CoV-2 uses the cell surface receptor ACE2 found in several tissues as the case with SARSCoV-1 [93]. As chloroquine could successfully inhibit SARS-CoV-1 it can be postulated that the drug may act on ACE2 receptor glycosylation hence inhibiting the binding of SARS-CoV-2. SARS-CoV-2 favors the acidic pH inside the lysosome which facilitates the release of virus from the shell for replication and transfer to infect other cells [94]. Chloroquine could interfere with the acidification trials of the virus to the lysosomes, hence preventing its replication [95].

All the previous data indicated that no successful treating for viral infections in human was reported. However, it was recently stated by Gao and his team that chloroquine improved the complications (e.g; pneumonia) of the viral infection in more than 100 patients; giving negative viral testing as well as shortening the infection period [96]. Hence, these promising results presented the success of chloroquine in humans, however extra clinical trials on larger samples including, different age classes as well as different stages of the disease. Additionally, strict rules about monitoring the drug outcomes should be taken in the normal patient site; hospitals to avoid the risks of patient self-treatment at home.

Hydroxychloroquine sulfate

Hydroxychloroquine sulfate was synthesized from chloroquine by adding a hydroxyl group. Fortunately, it showed less toxicity by nearly 40% compared to the parent drug [97]. Like the parent drug, hydroxychloroquine is used to treat malaria as well as autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis [98]. Hydroxychloroquine possesses nearly the same pharmacokinetics as chloroquine [99]. What makes hydroxychloroquine more favored than chloroquine is that it can be used in high doses for longer periods of time without causing any toxicities [100].

Hydroxychloroquine shares nearly the same mechanisms as chloroquine of being weak bases able to elevate the pH of the cell [101] as well as altering the ACE2 receptor glycosylation [102].

Clinical studies indicated that the plasma of COVID-19 infected patients contained high concentrations of cytokines [14]. As an anti-inflammatory, hence hydroxychloroquine can significantly reduce the production of cytokines so attenuating the associated inflammatory symptoms. Therefore, it can be concluded that hydroxychloroquine can act directly on the virus as well as combating its complications. Sharing nearly similar chemical structures, indications and mechanisms as well as referring to the achievements of chloroquine in dealing with SARS-CoV-2, so it is easy to evoke the idea of using hydroxychloroquine in treating SARS-CoV-2. Hydroxychloroquine was approved by the FDA in treating COVID-19 patients [103]. However, more confirmation by clinical investigations is required. Several clinical trials were done to test the efficacy of hydroxychloroquine in treating COVID-19 patients. Hydroxychloroquine improved the patients' case and fastened the recovery when compared to the placebo [104]. Additionally, it was observed that the drug succeeded in reducing the load of the virus or even its disappearance when co-administered with azithromycin [105].

In a clinical study performed on 62 patients infected with COVID-19, it was observed that patients treated with hydroxychloroquine showed shortened time for body temperature recovery as well as shortened cough remission time when compared to the control group. Additionally, the treated group was cured from pneumonia symptoms more than the control. On the other hand, 2 patients showed mild side reactions in hydroxychloroquine group [106]. Although the conducted clinical trials showed some promising results, however larger sample sizes are indicated.

Ivermectin

Ivermectin is a broad spectrum anti-parasitic drug approved by FDA for human use [107], it showed good *in-vitro* anti-viral activities against a wide range of viruses [108, 109]. Ivermectin was approved only orally in human with similar rate of absorption between solutions, suspensions and tablets [107]. The absorption of the drug shows an enterohepatic

cycle [110]. However in some patients the oral route doesn't provide the required therapeutic levels [111], hence a shift to another route e.g; parentral administration is required. The drug is widely distributed in the body due to its high lipid solubility [107]. The drug is extensively metabolized by first pass effect by cytochrome P450 [112].
Ivermectin inhibited the interaction of the human immunodeficiency virus-1 integrase protein (IN) with the importin (IMP) α/β1 heterodimer which account for IN nuclear import [113], hence inhibiting virus replication [109]. This effect was endorsed to the IMP α/β nuclear import inhibitory characteristics of ivermectin [109]. Additionally, ivermectin could limit the infection by RNA viruses [114]. Investigations on SARS-CoV proteins clarified the prospective role of (IMP) α/β1 during infection, which if inhibited could stop the division of the host cell [115-117]. Taken in consideration the role of ivermectin on inhibiting the IMP α/β nuclear import, hence it can be postulated that the drug may be effective against SARS-CoV-2. To approve the anti-SARS-CoV-2 activity of ivermectin, an *in-vitro* study on infected Vero/hSLAM cells was conducted which were treated with the addition of ivermectin. After 24 h, a significant reduction in the viral RNA could be observed in both the supernatant and the cell associated ones compared to the untreated cells [118]. This reduction increased after another 24 h and stopped on the 3rd day indicating the effective removal of all viral materials within 48 h without any cytotoxicity [109, 114].
These promising open the door for further investigations on the drug as a potential treatment for COVID-19 patients.

Conclusions

COVID-19 presented a global crisis affecting the economic and health sectors in all affected countries. The disease symptoms range from mild to severe, however its transmission from person to person is considerably high. The number of confirmed cases besides the number of deaths is continuously increasing. Unfortunately, up till now no specific vaccination or treatment have been developed which represents a serious problem requiring a quick solution to stop this pandemic. The WHO started an initiative called "WHO Solidarity Trial" to accelerate the production of an efficient vaccine. This review highlights the several trials carried out for the development of an efficient vaccine and medication. Also, the review sheds the light on some medicinal plants of specific properties as well as vitamin D which might help in the battle against COVID-19. Several repurposed drugs were discussed in details for example, remdisvir, favipiravir, oseltamivir, nelfinavir, chloroquine, hydroxychloroquine and ivermectin highlighting their pharmacokinetics, mechanisms of actions as well as the *in-vitro* and *in-vivo* trials carried out to test their efficacy. In conclusion, this review suggests reporting all the trials running in all world countries in peer-reviewed publications to help the international scientific community to extract and analyze the data which could guide the formulators of improving the drugs' dosing regimens based on the pharmacokinetic information and setting protocols for future clinical studies.

Declaration of interests: We declare no competing interests.

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