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The Ongoing Pharmacotherapy for Ministration of Covid-19 Disease: A Review

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Research Article

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ABSTRACT

A completely unique coronavirus (2019-n Cov) formally referred to as severe acute respiratory syndromes [SARS Cov 2] appeared in Wuhan, China. The coronavirus infectious disease 2019 (covid-19) has speechless like a shock in fully unprepared world. Covid-19 caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS Cov 2). Covid-19 first emerged in December 2019 all in cluster of patients with the pneumonia of unknown cause was recognized in Wuhan, China. In July 2020, SARS Cov2 was affected more than 200 countries. The coronavirus fevered 79% and 50% genomic similarities with severe acute respiratory syndromes coronavirus 2 [SARS Cov 2] and Middle East respiratory syndromes coronavirus [MERS Cov 2] respectively. Several drugs have been investigated for their efficacy and safety in the treatment of covid-19 disease like antiviral, antimalarial, antibiotics immunomodulators, and anticoagulants.

INTRODUCTION

On the date of March 11, 2020, the world health organizations announced that covid-19 was a global pandemic indicating significant global spread of an infectious disease [1-5]. The covid-19 disease caused by pathogen Nobel coronavirus (2019 Cov) which described by the International Committee on Taxonomy of viruses as the severe acute respiratory syndrome coronavirus 2 (SARS Cov2). The novel coronavirus born in Wuhan, China and has disseminated worldwide. The disease was declared as corona virus disease 2019 (covid-19) by world health organization on date of 11 Feb [6].

The etiology of the SARS Cov 2 is not clearly identified but somewhat similar as severe acute respiratory syndromes coronavirus (SARS Cov) [7]. The replication of virus and its components result into in vigorous inflammation and causes acute lung disorder. The high risk study of SARS Cov2 determined the fatality is uncontrolled pulmonary inflammation [8].

The novel coronavirus is the new strain that not found previously in humans. These viruses get named as the way they look under microscope [9]. The coronavirus involve core of genetic material surrounded by envelope with protein spike, that gives appearance of a crown, it means in Latin word corona means crown [10].

Peoples with covid19 have wide range of symptoms reported ranging from mild to severe illness. The coronavirus causes illness like respiratory disease. The respiratory disease ranges from common cold to more severe disease like Middle East respiratory syndrome coronavirus [11].

(MERS Cov) and severe acute respiratory syndrome corona virus (SARS Cov). The most of the covid-19 infected people feel little bit unwell, they will have a fever, they may have a cough and sore throat and sneeze [12]. In some individuals, they may have a gastrointestinal problem like vomiting and diarrhea, but they lead to be more mild and even most children tend to

have asymptomatic infections which means they don't have any symptoms at all. Some individuals also have symptoms like to decrease sense of smell and taste [13].

The coronavirus is single stranded RNA virus belongs to family coronaviridae, of the order of Niroviridae. In that four type of subfamily are involved: α, β, δ, γ which causes mild to severe respiratory tract disease. Coronavirus disease transmission occurred between the animals and humans; hence it is called as zoonotic. Some research study declared that SARS Cov transmitted from civet cat to humans and a MERS Cov was transmitted through dromedary camels to humans. The proper cause of SARS Cov2 not found yet but research is ongoing to investigate the zoonotic source to outbreak. There four structural protein involved in novel coronavirus: spike(S), membrane (M), envelope (E), nucleocapsid (N). Primarily the S protein in coronavirus responsible for entry of viral component into host cell by attachment of S protein to host cell. S Protein divided into two subunits that are S1 and S2, by action of host protease [14]. S1 Protein play important role in host cell binding and S2 in fusion of viral cellular membrane. Unlike coronavirus confess a miscellaneous of protease and entry receptor, where SARS Cov and SARS Cov2 processes their S Protein by utilizing cellular serine protease TMPRSS2 and consecutive interaction with angiotensin converting enzyme two cellular receptor.

Globally, there has been huge number of cases reported by world health organization. Worldwide there are 139,501,934 cases was confirmed and 29, 92,193 related death noticed on 14 April 2021 as per WHO report. A few year back, for controlling pandemic of Ebola virus, randomized trial are performed. But that time also many patients not cured [15].The scientist are disinclined the past mistakes into these current situations. The researchers from all over the countries try to find out therapeutically effective medicines to combat against novel coronavirus but still there is no any distinct medicines discovered to fight against these novel coronavirus. Many scientists from different countries have studied the effect of miscellaneous drugs on covid-19 patients. The drugs such as antiviral, antibacterial, antimalarial, anti-immunity boosters, anticoagulants also studied. Some of the scientist also conducted research on convalescent plasma therapy.

In this narrative review article we summarize the current pharmacological drug which shows greatest therapeutic activity with safety and efficacy with less adverse effect against novel coronavirus. This information may helpful to identify the specific treatment of covid-19 disease.

Clinically used pharmacotherapy of covid-19 disease

Antiviral drugs

Remdesivir

Remdesivir (veklory) was the first drugs approved by the food and drug administrations for treating the SARS Cov2 virus. Remdesivir is a prodrug of the adenosine triphosphate analogue, with potential antiviral activity against a variety of virus. It is an antiviral nucleotide analogue used for therapy of severe novel coronavirus disease 2019 (covid-19) caused by SARS Cov2 infection (Figure 1).

Remdesivir therapy is given by IV route of administration for 5 -10 days and is frequently accompanied by transient reversible, mild to moderate elevation in serum aminotransferases levels but has been only rarely linked to instances of clinically liver injury, its hepatic effect being over shadowed by the systematic effect of covid-19 [16].

Remdesivir has been studied in several clinical trials for the treatment of covid-19. The trial was carried out on 453 patients in the two groups of remdesivir and placebo designed for 28 days. The dose is 200 mg in 350 ml normal saline infused IV over approximately 30-60 min for the first day and 100 mg in 250 ml normal saline for 9 days [17].

On the May 1, 2020, the FDA provided use for remdesivir as the treatment of hospitalized covid-19 patients. Recently it was noted that for mild or moderate covid-19 patients, remdesivir not recommended. Remdesivir effectively inhibited SARS Cov2 infected Vero cells in vitro study [18]. Early administration of remdesivir showed a significant reduction in viral load in bronchoalveolar lavage compared to the vehicle and also decreases the pulmonary infiltrates in SARS Cov 2 infection of this macaque model. It demonstrates both antiviral as well as clinical effect [19]. Remdesivir found to be a potent inhibitor of SARS Cov2 replication in human nasal and bronchial airways epithelial cells [20].

Adverse effect of Remdesivir

Common adverse event noted use of remdesivir in patients with covid-19 include rash, diarrhoea, hypotension, abnormal liver function and renal impairment. Serious adverse event (acute kidney injury, septic shock) noted 23 % [21].

Favipiravir

Favipiravir is a purine nucleotide analogue included instead og guanine and adenine (Figure 2). Favipiravir is a prodrug which when administered into human body, it get metabolized into its active form favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP) [22]. Favipiravir is administered in two forms: oral and intravenous. In japan, favipiravir was developed for treatment of resistant influenza virus and also other infections. The Toyoma chemical from Japan country manufactured and developed favipiravir and gets approved to use for medicinal purpose [23]. In 2019, its patent is over and it comes under category of generic drugs.

The clinical trials on favipiravir were conducted in Shenzhen. Initially 80 patients get selected and it observed that chest x ray imaging recovered at higher level (62%) and viral clearance time get reduced (91.43%) [24]. Afterwards study was going on 120 patients, in that efficacy with 7 days clinical improvement rate of 71.43% and decreased cough and pyrexia [25].

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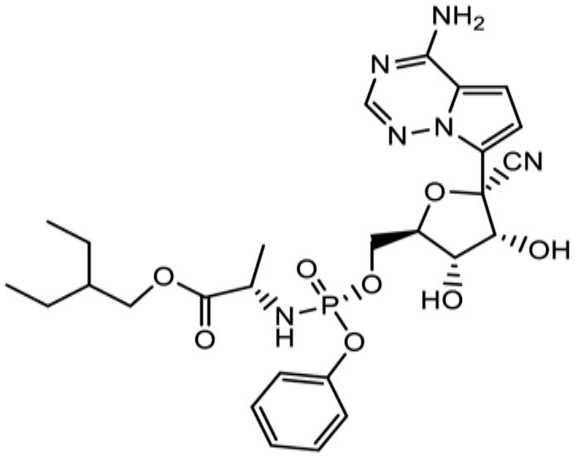

Figure 1. General structure of Remdesivir

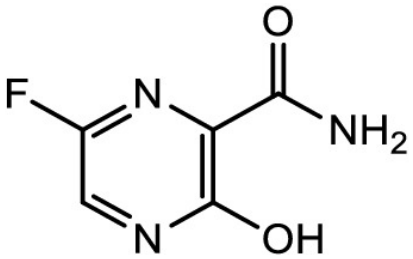

Figure 2. General structure of Favipiravir.

Favipiravir is a broad spectrum antiviral drug with evidence based research on its efficacy of antiviral activity in several human RNA virus like Nipah virus, Influenza virus, Ebola virus, Lassa virus, and rabies [26-28]. The favipiravir prevent viral transcription and replication by binding of active form of favipiravir that is favipiravir-RTP to the RNA dependent RNA polymerase (RdRp) and inhibit it [29].

In these mechanism, the incorporation of favipiravir-RTP into a newly formed RNA strand [30] preventing its elongation and proliferation of viral genome. The competitive binding of RNA dependent RNA polymerase by the favipiravir-RTP and purine nucleosides which ultimately affects viral replication and transcription [31, 32].

The review study suggested that rate of viral clearance is much faster than in umifenovir and lopinavir/Ritonavir [33, 34]. The favipiravir was became almost potential drug treatment for covid-19 patients due to resemblance of RNA structure of SARS Cov2 with SARS Cov [35].

Antibiotics

Azithromycin

To moderate patients UN agency took HCQ alone or with azithromycin. A study on 1061 patients in France, during which a gaggle of patients received HCQ and azithromycin, showed that the employment of that medication may be safe once the complications of COVID-19 failed to occur within the patients. During this case, a discount in mortality occurred within the patients. Azithromycin is AN antibiotic derived from the macrolide Pediamycin. This antibiotic has shown higher performance than Pediamycin against gram-positive and gram-negative pathogens. In one study, the connection was investigated between macrolides and mortality in MERS-CoV patients [36]. The results showed no important relationship between macrolide treatment within the patients and reduced mortality [37].

However, the treatment of COVID-19 patients with azithromycin cannot be avoided as a result of the amount of studies with similar results is tiny. Azithromycin has been employed in several reports examining the consequences of HCQ [38]. In a very study on eighty patients, azithromycin and HCQ were wont to treat COVID-19 that considerably reduced the microorganism load within the patients [39]. Within the US, a retrospective study was going on the history of hospitalized patients with COVID-19.

Mortality was lower within the cluster receiving HCQ using azithromycin than within the cluster receiving HCQ alone. In another study, the employment of HCQ with azithromycin was involved in reducing the mortality of COVID-19 patients [40]. What is more, adding azithromycin to the medication program of patients taking HCQ and LPV-RTV improved the overall condition of the COVID-19 patients.

In a systematic study victimization meta-analysis, there was no important distinction between HCQ recipients and also the management group; but, in some cases, HCQ in conjunction with azithromycin reduced the progression of respiratory organ illness [41] In 5 studies, the employment of each HCQ and azithromycin was related to improved outcomes yet, in a very controlled trial,

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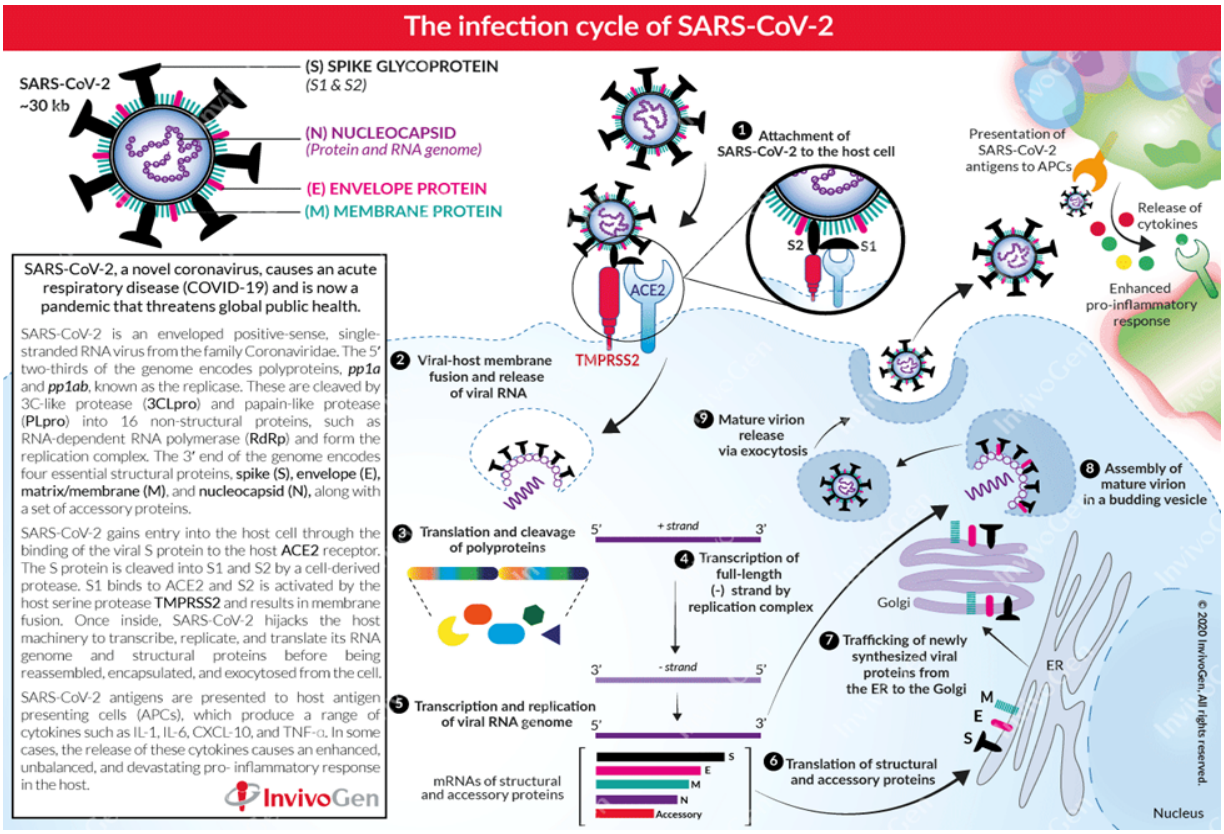

Figure 3. The Infection Cycle of SARS-COV-2.

COVID-19 patients were treated with HCQ alone or with azithromycin [42-44]. Compared to the management cluster, no improvement in clinical standing was discovered in delicate.

Teicoplanin

In 2016, a study begins that glycopeptide antibiotics were applicable for diseases like infective agent viral infection, SARS-CoV, and MERS-CoV due to their low toxicity [45]. In another study, teicoplanin functioned as Associate in Nursing matter of infectious agent virus infection to advance the healing method [46]. In reality, teicoplanin inhibits the virus entry by inhibiting cathepsin L Teicoplanin, that's related for infectious cases, was suggested in degree very study for COVID-19 treatment. However, the role of teicoplanin in inhibiting novel coronavirus remains to be processed [47].

The SARS-COV-2 Infecton Cycle

Angiotensin-converting catalyst a pair of (ACE2) may be a cellular receptor expressed within the lungs, arteries, heart, kidneys, and also the internal organ (Figure 3). ACE2 binds to the infective agent (S) super molecule and constitutes the cellular entry receptor for SARS-CoV-2 into their human host [48]. Specifically, the S super molecule is cleaved into 2 subunits, S1 and S2, by Associate in nursing living thing proteinase. Whereas S1 binds to ACE2, S2 is any cleaved and activated by the host surface-associated Trans membrane proteinase aminoalkanoic acid a pair of (TMPRSS2) [49]. Along these actions end in host-viral membrane fusion and also unless of the ribonucleic acid order into the host cell protoplasm [50, 51]. Firstly, the host travel machinery is hijacked for the interpretation of the poly proteins and also the essential infective agent proteases [52]. The poly proteins (pp1a and pp1ab) square measure cleaved into sixteen non-structural effector proteins by 3 CLpro and PLpro permitting them to create the replication complicated along with the ribonucleic acid-dependent RNA enzyme, that synthesizes a full-length negative ribonucleic acid strand template [53,54] this is often wont to replicate the whole ribonucleic acid order and generate the individual sub-genomic template RNA templates required for the interpretation of the infective agent structural and accent proteins [55]. The freshly synthesized structural and accent proteins square measure then trafficked from the ER through the Golgi body, when that new virions assemble in budding Golgi body when that new virions square measure exocytosed and free from the host cell into the encompassing atmosphere to repeat the infection cycle [56,57].

Indian medicinal plants against Covid-19

Nigella sativa (black cumin)

Nigella sativa L.'s bioactive compounds are saw as potential inhibitors of COVID-19 in molecular arrival studies. Nigellidine provided energy advanced at situation (6 LU7) with energy scores highest to antimalarial and higher than anti-inflammatory and favipiravir whereas α-hederin gave energy advanced at the situation (2 GTB) with energy scores higher than antimalarial, anti-inflammatory, and favipiravir [58]. The alcoholic seed extract has shown immunological disorder activity on a phyto hemagglutinin

and immune stimulating result on non-phyto hemagglutinin (PHA) stirred proliferation [59]. The thymoquinone-rich oil showed suppression of protein sign molecules, and PGE2 in T-lymphocytes moreover as increased PGE2 unleash in adreno carcinomic human alveolar basal animal tissue A549 [60].

Linium Ussitatissium (flax seed)

Hetero polysaccharide, extracted from flax seed hull obsessed immune modulatory activity and anti-hepatitis B virus potential. It suggestively aroused mRNA expression of TNF-α, NO and IL exhibiting immune responses in murine macrophages. Antiviral activity has been rumored through inhibition of expression of surface matter moreover as wrap matter and conjointly interfered with DNA replication. The study urged its promising potential as associate immune stimulant and immunogens adjuvant [61]. It showed medicine and immune modulatory potential in obesity-associated endocrine resistance. Its oil in co-culture with 3T3-L1 adipocytes-RAW 264. 7 macrophages of C57BL/6 mice rumored shifting the cytokines toward medicine with a decrement in TNF-α. Immunomodulation has been determined through a rise in levels of Th2-related protein (IL-4), bodily fluid anti-ova IgG1, and IgE, and a decrease in Th-1 connected cytokines (TNF-α and IFN-γ) and anti-ova immunoglobulin levels [62]. Another study rumored the immune modulatory activity of phenoplast parts of flax seed principally through reduction in cell-mediated immune responses [63].

Withania Somnifera (ashwagandha)

Multiple studies have established that Ashwagandha has antiviral and immune modulatory potential. terribly recently, associate in silico study complete that Withaferin-A exhibits antiviral potential against SARS-CoV-2 through inhibiting ribonucleic acid enzyme with higher separation energy than anti-inflammatory and different medication used against SARS-CoV-2. Another study on withania one showed blockage of SARS-CoV–2 entry and conjointly its subsequent infection by interrupting electricity interactions between the RBD and ACE2 [64]. Grover and colleagues through molecular arrival reportable the potential of withaferin A against HSV through inhibition of deoxyribonucleic acid enzyme protein [65]. *Withania somnifera* molecular mechanism has been elucidated by exploitation network ethnopharmacological technique and reportable that withanolide-phytosterol combination may be a smart immunomodulator [66]. W. *somnifera* formulation (supplemented with minerals) has been reportable to enhance each cellular and body substance immunity further as medical specialty profile additionally to the numerous inhibitions in mouse splenocytes [67]. Liquid root extract of W. *somnifera* attenuates production of pro-inflammatory cytokines and transcriptions think about collagen-induced inflammatory disease. A study in 2018 showed that W. *somnifera* considerably stifled RNA expression of inflammatory proteins and promotes the RNA expression of the medicine cytokine in HaCaT cells.

CONCLUSION

This review aimed to current treatment choices in combating SARS-CoV-2. Based on several aspects, it may be complete that remdesivir and anti-inflammatory with or while not azithromycin ar still treatment choices for COVID-19 patients within the gentle to moderate stages of the malady. The World Health Organization declared the happening of novel coronavirus" A public health Emergency of International concern" on January 30. On March 11, 2020 after sustained unfold of the malady outside of china, and currently round the World, will hopefully blunt the spread of the virus whereas treatment and a vaccine are developed to prevent it.

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