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Comparison Between of Five Drugs Anti-Virus for COVID-19th in Chemicals Properties and Pharmacological Effectiveness: A Review

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KEY WORDS
Remdesivir
Hydroxychloroquine
Favipiravir
Vaccine

Abstract: The corona virus epidemic outbreak has urged an extreme worldwide effort for re-purposing obtainable approved medications for its treatment. In this review, we're focusing on the chemicals properties and pharmacological effectiveness of medications of small molecule that are presently being evaluated in clinical trials for the management of corona virus (COVID-19). The current review sheds light on a number of drugs that have been diagnosed to treat COVID-19 and their biological effects.

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INTRODUCTION

In the mid-end of December 2019, several cases of pneumonia outbreak of unknown cause and etiology were identified in Wuhan City of Hubei province In China, Later, on 12th January 2020, this coro-navirus was named as 2019-novel coronavirus (2019-nCoV) by World Health Organization (WHO) and in 11th February 2020 COVID-19, is a single-stranded RNA beta-coronavirus whose genome encodes are structural proteins, non-structural proteins and accessory proteins[1]. Internationally, the virus already had infected 413,467 individuals and about 18,433 persons have passed away by 25 March, 2020 (2) and the fatalities are rising exponentially. In the meantime, only 113453 patients have recovered which is 27.45% of total affected population[2]. The characteristics of the infected population are already published[3, 4]. Several treatment protocols have been advised and used for controlling COVID-19 on the basis of earlier practices with other viral infections such as Ebola virus, malaria and cholera virus[5] (Table 1-4).

Aim: The aim of this article is to compare for five types of drugs that have been diagnosed as a treatment for COVID-19 virus, through chemical characteristics, biological effectiveness, therapeutic safety as well as

Table 1: Chemical properties for the five drugs

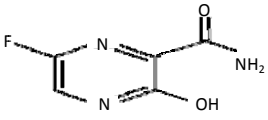
IUPAC name	Molecular formula	Common name	Structure
5-fluoro-2-oxo-1H-pyrazine-3-carboxamide	$C_5H_4FN_3O_2$	Favipiravir	

Table 1: Continue

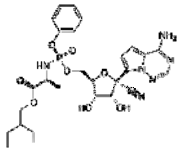
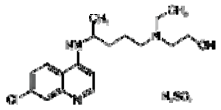
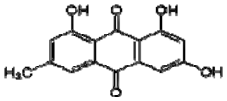
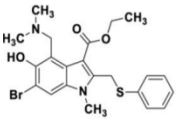
IUPAC name	Molecular formula	Common name	Structure
Propan-2-yl (2S)-2-[[[(2R,3R,4R,5R) -5-(4-aminopyrrolo [2,1-f][1,2,4] triazin-7-yl)-5-cyano-3,4-dihydroxy-4-methyloxolan-2-yl] methoxy-phenoxyphosphoryl] amino]propan	$C_{25}H_{31}N_6O_8P$	Remdesivir	
2-[4-[(7-chloroquinolin-4-yl) amino]pentyl-ethylamino]ethanol	$C_{18}H_{26}ClN_3O$	Hydroxychloroquine	
1,8-Dihydroxy-3-(hydroxymethyl)-9, 10-anthraquinone	$C_{15}H_{10}O_5$	Lianhuaqingwen	
Ethyl 6-bromo-4-[(dimethylamino) methyl]-5-hydroxy-1-methyl-2-[(phenylsulfanyl)methyl]-1H-indole-3-carboxylate[6]	$C_{21}H_{25}N_2BrO_3S$	Arbidol	

Table 2: Biological test results for the five drugs

No. of drugs	Biological test results
1	It hinders RdRp(RNA-dependent RNA polymerase) selectively, an enzyme required for the viral duplication of RNA inside man cellular system. It acts as a purine equivalent and is integrated as an alternative to amino-hypoxanthine (guanine) and 9H-Purin-6-amine (adenine). The integration of a solitary molecule of Favipiravirends the RNA lengthening (viral elongation). The medication is transformed intra-cellularly into its dynamic phosphorylated formula and is then recognized as a substrate by viral RNA-dependent RNA polymerase(RdRp). It has a broad-spectrum activity to RNA viruses (flu virus, Rhino and Respiratory Syncytial Virus etc.) but not against DNA viruses(such as HSV[7] herpes simplex virus))) In Influenza virus, the valuable outcomes were credited to a decline in pulmonary viral loading and tumor necrosis receptor (TNF-alpha)points in the airways[8]. It was utilized as a post-exposure prophylactic drug and for treating of Ebola-infected patients and has also been chosen for treating humans with Lassa hemorrhagic fever (Lassa fever LHF), Rabies and Norovirus infections[9]. The permitted Favipiravirflu curing dose in Japan is 1600 mg two times on 1st day and 600 mg two times per day for four days more. For Ebola viral infection the dose is 6000 mg on the 1st day and 2400mg for 9 days more[10]
2	As an antiviral pro-drug and a nucleotide analogue, remdisivir requires bioactivation within cells[11] The active remdesivir molecule in cells is a tri-phosphate with its most significant activeness is the inhibitory effect on RdRp. The active tri-phosphate is actually a tri-phosphate of GS-441524 (C-nucleoside with ribose linked to the nucleobaset hrough a link (bond) made between two carbons) that is the final product of the remdesivirinitiation. Nevertheless, the stimulation is a furthermultifariousprocedureconcerning an esterase that eliminates the ester of 2-ethylbutanol and 2-aminopropanoic acid in the lipophilic part of remdesivir. This is tracked by an intra-molecular reorganization, leading to alanine remainder connection to the phosphoric acid moiety through nitrogen (in this way developing phosphor-amide). This is accordingly condemned by a phosphamides-developing nucleoside mono-phosphate which is as a final pointtriggered to the tri-phosphate by nucleoside-phosphate kinase. The nucleoside mono-phosphate might be tainted to a nucleoside which in sequence can undergo rephosphorylation again through kinases[12, 13]
3	Because this drug is a weak base that is being accumulated within acidic intra-cellular sections, such as lysosomes[14]. When used at high concentrations, hydroxy-chloroquine appears to cause a dose-dependent increasing in the endosomal as well as lysosomal Ph[15, 16]. In contrast, low hydroxy-chloroquineconcentrations may employ a separated immunomodulatory consequence on intra-cellular innate immune responses to viral infections with least interference in lysosomal activity[17, 18] The combination of the alkalization of the endolysosomalpath and the immunomodulatory effects of hydroxy-chloroquine have caused suppositionsadjoining their probable benefits in the treating of viral infections. Although both innate and adaptive immune responses are vital to retrieval from viral infections, excessive activation of immune responses may cause serious tissue destruction and disease advancement. Such counterproductive immune responses have been observed in chronic Human Immunodiffiency Virus (HIV)[19], severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 infections[20], resulting in investigation of hydroxy-chloroquine and chloroquine as possible immunomodulatory treatments
4	LianhuaQingwen has been advised by the National Administration of TCM (Traditional Chinese Medicine) as an inhibitory and curative medication of contagious diseases in the ventilatorysystem. European respiratory society -COVID[21] has a definiteres training outcome. Lianhua Qingwen pills (particles) can hinder viral infections through direct and indirect paths

Table 2: Continue

No. of drugs	Biological test results
	The direct pathprimarilyinfluences the function of the viral envelope, constrainsthe adsorption of the virus and its intracellular diffusion and impedes viral transcript and duplicationprocedures. Indirect paths comprise expanding body invulnerability, expanding levels of Ig(immunoglobulin), regulation of cytokine production and releasing and hindering of viruses-initiated oxidative stress damage, etc.[22]. Furthermore, Lianhua Qingwen capsules (particles) also comprise notable outcomes clinically in anti-pyretic, cough and phlegm exclusion and anti-bacterial and anti-inflammatory outcomes[5]. Along with the estimation of action objectives, Lianhua Qingwen contains twenty two core targets for 2019-nCOV, mostly including inflammation mediators and MAPK (mitogen-activated protein kinases)[23]. Various clinical interpretations of Lianhua Qingwenin collaboration with predictable managements are capable of increasing the disappearing degree of main signs of NCP (fever, coughing, tiredness) and further signs (chest tightness, shortness of breath "dyspnea" and appetite loss), in addition to severe symptoms proportion declining
5	Arbidol is a broad-spectrum antiviral medication that has been permitted in numerous nations[24]. The anti-viral mechanism of this medication is primarily in this way: a) reticence of the membrane union between viral elements and plasma membranes, b) organizing of the immune reaction by generating IFNs (interferons) and white blood cells (macrophages) activation. c) inflection of the inflammatory cytokines manifestation such as IL-6 (interleukin-6), IL-8 (interleukin-8) and tumor necrosis factor alpha (TNF α)[25]. New researches have more over-revealed that Arbidol has antiviral outcomes on other viruses like HSV (herpes), ZIKV (Zika fever) and EVD (Ebola virus disease)[26]. In the laboratory, the efficacy of Arbidol in hindering severe acute respiratory syndrome (SARS) corona-virus duplication has been confirmed and detection researches have described the encouraging influence of this drug on the management of corona virus[27]

Table 3: Safety for the five drugs

No. of druges	Safety
1	Safety concerns have been taken place regarding using favipiravir including QTc interval elongation which were upturned in laboratory and pharmaco-dynamic revisions[13]. Transient increase in acid urates (uric acid) levels in stage 1-3 safety researches have also been reported[28] with indication of a dose-dependent aggregation trend. Remarkably, 2 stage 3 RCTs (n = 2547) statedan increase in acid urateslevels that resumed to regular serum concentrations before the twenty one-day trial cutting-off. No signhas confirmed gout (hyperuricaemia) produced by Favipiravir result in clinical exhibitions; nevertheless, longer trial following-up stages would be mandatory to completelyevaluating this risk[29]
2	With increasing use, adversative outcomes of remdesivir have been spotted and develop a clinical issue. These adversative effects include a transitory rising in serum amylase was testified in an EVD-diseased patients received remdesivir treatment[30] Grein etc. study declared rashes, MODS (Multipleorgan-Dysfunction Syndrome), DVT (Deep-Vein Thrombosis), acute confusional state (delirium), septic shock and fever (pyrexia) as adversative occasions arisen in remdesivir receivers[31]. Adversative occasions associated with hematologic, circulatory, endocrine and other systems were also identified in the remdesivir group in the RCT in China. The existing safety profile of remdesivir is yet not completed. Accumulative evidence has observed COVID-19 is concerned in multiple organs injuries including lung, liver, gastro-intestinal tract, cardiac and renal injuries[32]
3	In a consequent large double-blind clinical trial, 81 SARS-CoV-2 diseasedindividuals randomized to either low (450 mg twice daily on the 1stday and once daily for 4 days) or high dose (600 mg twice daily for ten days) chloroquine were compared with both groups also treated with the antibiotic azithromycin. Increased morbidity from cardiac effects related to an elongation of the corrected QT interval was detected on electrocardiography in the high dose group[33] A daily dose of >5 mg/kg/day over anextended period was deliberated to confer a greater risk of hydroxychloroquine retinopathy[34] and safe dosing guidelines for chronic usage of hydroxy-chloroquine were demarcated by this threshold[35]. Due to the risk of hydroxy-chloroquine retinopathy following chronicconsumption, screening programs were advised in numerous countries to shrink the risk of permanent visual loss in this group[36]
4	Several studies suggested LH as a symptoms improving drug for patients with covid-19, such as fever, fatigue and muscle ache. But it's important to know that safety is still uncertain[37]
5	Arbidol (Umifenovir) impedes the viral combination with the host cell by abolishing the hem agglutinin and Stimulation of the immune system and increasing the macrophages phagocytic activity by IFN (Interferon) making. This medication has a hepatic metabolism and is being consumed at a dose of 200 mg every eight hours. The dynamiccomponent of this medication is non-poisonous and it infrequentlyproduces adverse effects

Table 4: Toxicity for the five drug's

No. of druges	Toxicity
1	According to previous studies,There is an indication that Favipiravir has teratogenicprobability. To alleviate the unclear teratogenic risk, the drug approval system in japan recommends that Favipiravir need to be prescribed with a sturdy caution against usage in women of reproductive age and acclaims to be packaged and prescribed with precautionary statements. The system also acclaims that Favipiravir should not be used where differentmedicines could be administered
2	Researches of toxicity of remdesivir in animals showed no hepatic changes, where as provisional treatment-emergent rises in transaminases (aminotransferases) were detected in clinical studies of remdesivir[38]. In a case series, greater transaminases (aminotransferases) levels after Remdesivir introduction were detected in 3 corona-infected individuals[39]. Lescure *et al*. also stated 1 COVID-19 infected individual dropped Remdesivir because of increased ALAT (Alanine amino-transferase) and

Table 4: Continue

No. of drugs	Toxicity
	skin rash which then declined within three days[40]. Gastrointestinal symptoms: COVID-19 patients treated with remdisivir have been experienced gastrointestinal symptoms including nausea and one ached from gastro paresis following the initiation of treatment. Diarrhea was detected in nine percent of the patients which were administered remdesivir in Grein *et al*.'s study. Dependent on a Chinese RCT, a greater ratio of remdesivir administered individuals than placebo administered individuals had dosing impulsively stopped due to anorexic symptoms, nausea and vomiting[41]
3	Although, the first cases of retinopathy accompanying chloroquine treatment were labeled in the late 1950s[42], retinal toxicity was considered uncommon until the turn of the century as only patients with symptoms of hydroxy-chloroquine retinopathy were spotted[43]
4	Several studies described adversative reactions, comprising diarrhea, skin rash, gastro-intestinal reaction, headache, nausea, vomiting, abnormality in hepatic function and kidney dysfunction[44]
5	Arbidol adverse effects include eczema (dermatitis), gastro-intestinal symptoms (such as nausea and diarrhea), icterus (jaundice) and neurological signs were not detected in any of the patients following two weeks. Nevertheless, it should be avoided in children <2 years of age and pregnant and breast feeding women. Cautionary observing of its adverse outcomes must be performed in individuals with hepatic and renal dysfunctions. The LD50 dose of this medication is four gram per kilogram of body weight[45]

from the toxicological point of view of these drugs and to reach the reasons that make preference for one drug over another with in this drug group proposed in Its use is a cure for COVID-19 virus.

CONCLUSION

After the scientific the reviewer for five of the medicines used to treat coronavirus in terms of chemical properties, biological effect, safety and security, it was revealed from the viewpoint of the researcher that the compounds bearing the group (NH_2) as well as the halide (Br) is more electronegative and with the presence of the element sulfur (S) in the chemical formula of this drug with less toxicity and effect The treatment and overcoming the virus are higher and safer. Therefore, the ArbidolIt is the drug most likely to be used and then a Favipiravir. While excluding the Remdesivir, Hydroxychloroquine and lianhuaqingwen are high negative effects.

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