Al-Nahrain Journal of Science
Special Issue: COVID-19, April 2020, pp. 6 – 11

An Overview of Possible Therapeutic Approaches Against Novel Coronavirus Disease 2019 Pandemic

Mohammed H. Al-mashhadani[1,*], Raghda Alsayed[1], Zainab Hussain[2], Nadia Salih[3], Emad Yousif[1]

[1] Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq.
[2] Department of Chemistry, College of Science, Misan University, Misan, Iraq.
[3] School of Chemical Sciences and Food Technology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor Darul Ehsan, Malaysia.

Articles Information

Received:
22.4.2020
Accepted:
02.5.2020
Published:
16.5.2020

Keywords:
Coronavirus
COVID19
ivermectin
SARS-COV2
Iraq

Abstract

The fatal disease (COVID19) is produced by SARS-COV2. It caused a hug global problem due to causing of killing ten thousands of people around the world and almost stopped the world economy causing great economic problem. This is because of the quarantine in many countries around the world. Up to date, researchers believe that COVID19 has transferred from animals like bats or rodents to the humans and spread around the world by person to person direct contact, coughing, or sneezing. Many therapeutic approaches have been utilized to stop this pandemic from spreading around the world hence almost of the strategies showed a moderated results against the virus. Blood plasma of recovered people have been utilized as medication approach by few doctors in China via injecting the plasma to the infected people, this approach has demonstrated positive results against the virus. This review includes a highlighting of some medications which have shown promising results especially if it will link with other type of drugs such as Ivermectin.

DOI: 10.22401/ANJS.00.3.02

* Corresponding author: mo_chemical@yahoo.com

1. Introduction

The outer surface of coronavirus has crown-like spikes, hence the virus was known as a coronavirus which is belong to the coronaviridae family. The virus has four subgroups which are alpha, beta, gamma and delta. Coronaviruses have only single RNA in its genome of nucleic acid and its size is very small, the diameter between 65 to 125 nm and the length of nucleic acid between 26 and 32 kbs as shown in Figure 1. In the beginning it was thought that beta coronavirus effects only animals till it was noticed some cases in 2002, China which was infected people with severe acute respiratory syndrome (SARS) [1]. After about ten years another subgroup of coronaviruses spread wide in the Middle East countries, called Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Lately at 2019, Wuhan evolving business center of China outbreak of a novel coronavirus 2019 (COVID19), which have killed about two thousand individuals within only first fifty days of the virus spreading and infected more than seventy thousand people. The disease has been named COVID-19 and the virus as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV). Chinese researchers named this type of coronavirus by Wuhan coronavirus because it's first witnessed in this city and they also call it COVID19 which is abbreviation for coronavirus disease 2019. COVID19 is a beta subgroup of coronavirus family [3–5].

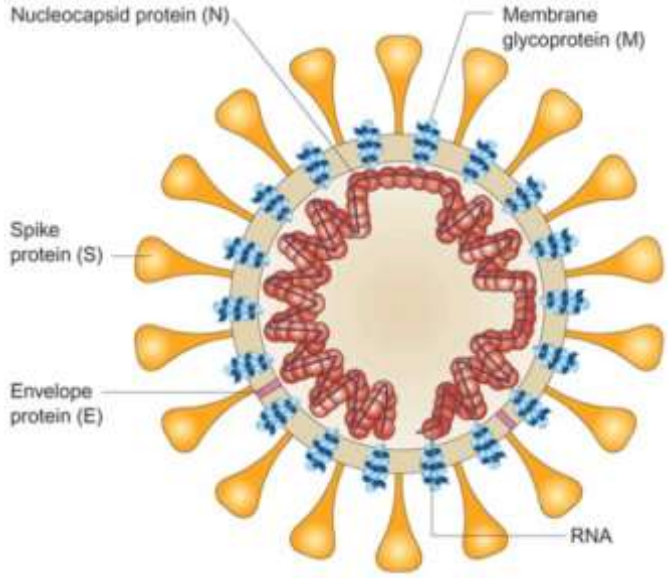

Figure 1. Structure of SARS CoV-2 Virion [6].

2. SARS CoV-2 hosts and sources

The reservoirs of beginning and transmission of coronavirus 2019 are significant to be investigated in order to improve protective approaches to surround the virus infection. Both rodents and bats seem like having got ability to host different types of coronaviruses and this looks a mystery [7-8]. After witnessing SARS in host bats, they have been tested heavily for COVID19. It has also sampled other host animals, however up to date writing this report, bats are the major source of coronavirus as shown in Figure 2 [9-11].

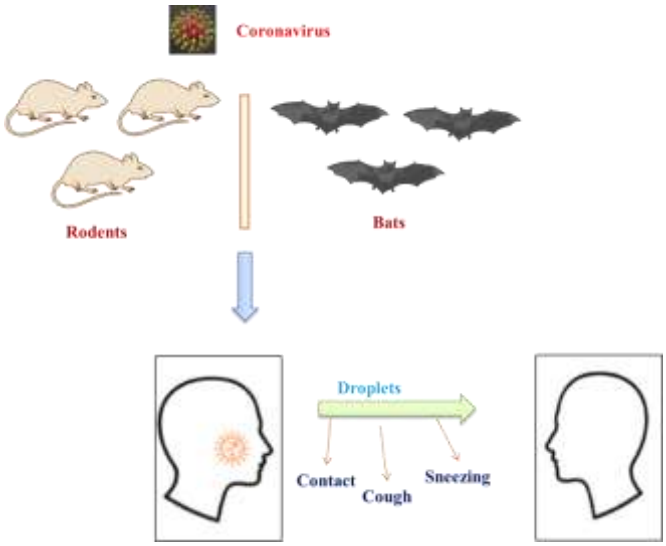

Figure 2. Schematic diagram of key source SARS CoV-2 and how transfer to humans.

The subgroups alpha and beta are the only types which have the ability to transfer to humans from animals and affected them. The main reservoir of the virus transferring to humans is by consumption of host animals as a food then the virus transfer between people due to direct contact, sneezing, or coughing as shown in Figure 2.

3. Possible medication approaches against SARS CoV-2

As we know, the SARS-CoV-2 RNA is surrounded by lipid bilayer and protein envelopes. The Spike (S) protein present on the envelope binds to a cell membrane receptor named as angiotensin converting enzyme (ACE2), thus SARS-CoV-2 initiates human cell entry. After that, the two subunits cleavage of S protein ;by a human cell-derived protease thought to be Furin; are produced which are : S1 and S2.

Then , S1 binds to its receptor, ACE2 while the other fragment, S2, is cleaved by another human cell surface serine protease called TMPRSS2, resulting in membrane fusion. Therefore , it is believed that both ACE2 and TMPRSS2 are thought to be essentials in airway cells for SARS-CoV-2 infection [12,13]. Anti-viral, interferons-a nebulization, were utilized to decrease viral load [14-15], hence remdesivir has demonstrated promising results against coronavirus. Remdesivir or Remdesivir combined with chloroquine were worked to stop SARSCoV- 2 replication [16-17], Chloroquine can inhibit pH-dependent steps that are essential for several viruses replications [18] Chloroquine showed through several studies that inhibited through the glycosylation of cellular receptors of SARS-CoV [19-20]. This medicine was used for Iraqi patients many times, other medications were also used against the virus such as lopinavir and ritonavir, were utilized to HIV infection. In Korea, it has been showed, ß-coronavirus viral loads of a COVID-19 patient obviously cut-down after lopinavir/ritonavir treatment [21]. Ribavirin is a guanosine analog that interferes with the RNA and DNA replications of viruses. The ribavirin structure also impacts RNA capping which affects natural guanosine thus prevents RNA degradation. On the other hand, Ribavirin inhibits natural guanosine generation resulting in further destabilization of viral RNA, also in a pathway that is vital for the guanine precursor production to guanosine; it directly inhibits inosine monophosphate dehydrogenase. Although when treatment with Ribavirin is blocking the virus from replicating incompletely, reduced replication fidelity of the viral nucleic acid occurs which results in random mutations that reduces the virus viability [22].

Umifenovir (brand name Arbidol) was used for influenza infection treatment in Russia and China. It was obvious that it is more effective in preventing RNA viruses infections than DNA ones. The drug stimulates the humoral line of the immune system, producing interferon, and stimulating the macrophages phagocytic response [23]. Remdesivir (GS-5734) proves a wide-spectrum antiviral activity when used versus SARS coronavirus and MERS coronavirus which are considered as RNA viruses. Simply, its antiviral activity results from the interfering with RNA polymerase and exoribonuclease (ExoN), causing the viral RNA production to decrease [24]. Further conclusions were submitted by National Institutes of Health at USA, showing that remdesivir was effective in minimizing the recovery time from 15 to 11 days in patients with COVID-19 serious infection [25]. The European Medicines Agency (EMA) started a 'rolling data review' on the use of remdesivir in COVID-19, this rolling started on April 2020 [26]. All these drugs show moderate outcomes once verified against the virus in-vitro clinical isolate patients [27-28]. Recently doctors in Shanghai successful to isolate blood plasma from recovered patients and injected to the infected patient and it was presented positive results [29-30]. Convalescent plasma is basically the liquid blood component that taken from patient who has recovered from a disease, which is in this case COVID-19. Researchers nowadays are racing to set up clinical studies to be more confident in case the treatment is useful, this may lead to FDA approval to widen the range of use. As a response, normally the body immunity creates proteins called antibodies that combined to parts of the pathogen and in this way stop the infection. This antibody response could be known as an acquired immunity ,also can be considered as another synonym of convalescent plasma .Antibodies can be provided immediately, & no clear evidence on how studies give such benefit in contrast to a placebo. This also applies to the first studies which used plasma for COVID-19 treatment.. Among these studies, and after entering a hospital in Shenzhen , China, five patients with severe COVID-19 disease along with (oxygen therapy, intubation, infusion pump or intravenous fluid) were injected with convalescent plasma 10 to 22 days. Three of the patients were discharged at the end of March, and two were in stable condition 37 days after plasma transfer [31]. For the U.S. clinical studies, neutralizing antibodies content in the donated plasma considered as crucial point. The Data reveals that may be these antibodies prohibit the virus from reaching a host cell and therefore prevents the infection by indicating that the spike protein, a specific protein in SARS-CoV-2, has been used by the virus to link human cells proteins in order to enter, is a target of neutralizing antibody [32]. Early on within the infection, the infection is tainting cells and sequesters cell technology to create numerous duplicates of itself. “But as the disease progresses, the tissue damage done by the virus is more difficult to reverse and isn’t necessarily reversed by something that is solely targeted towards the virus itself,” such as antibodies. It doesn't necessarily imply that acquired antibody therapy with COVID-19 wouldn't help someone who's so ill. In other countries, clinical studies of convalescent plasma are on the way. As doctors wait for answers from the finished studies.

The effectiveness of the Ivermectin drug in the treatment of COVID-19. Researchers from Australian Monash Univeristy in Melbourne reflected that a single dosage of the medicine,, Ivermectin, could block the growth of the SARS-CoV-2 virus in cell culture - effectively terminating all the virus's genetic material during 48 hours [33-34].

In spite that, the pathway by how Ivermectin acts against this disease is not well understood, depending upon its behavior in many viral infections, it is expected to discourage the virus from frustrating the host cells to remove it, Dr Wagstaff said (see Figure 4) [35-36].

4. Conclusions

SARS CoV-2 is a dangerous virus that was discovered at the end of 2019 in China, and scientists have not been able to find a treatment or vaccine for this virus, but they have used some therapeutics which has proven successful in treating against COVID19 within 48 hours such as Ivermectin. Isolated blood plasma from recovered patients was also utilized as a treatment by injected the plasma to the infected patients. This approach has shown a positive result against the virus. In summary, up to date there are many medications for COVID19 thus they proved moderated influence against the disease. All available therapeutics may need to combine with other drugs to show promising results.

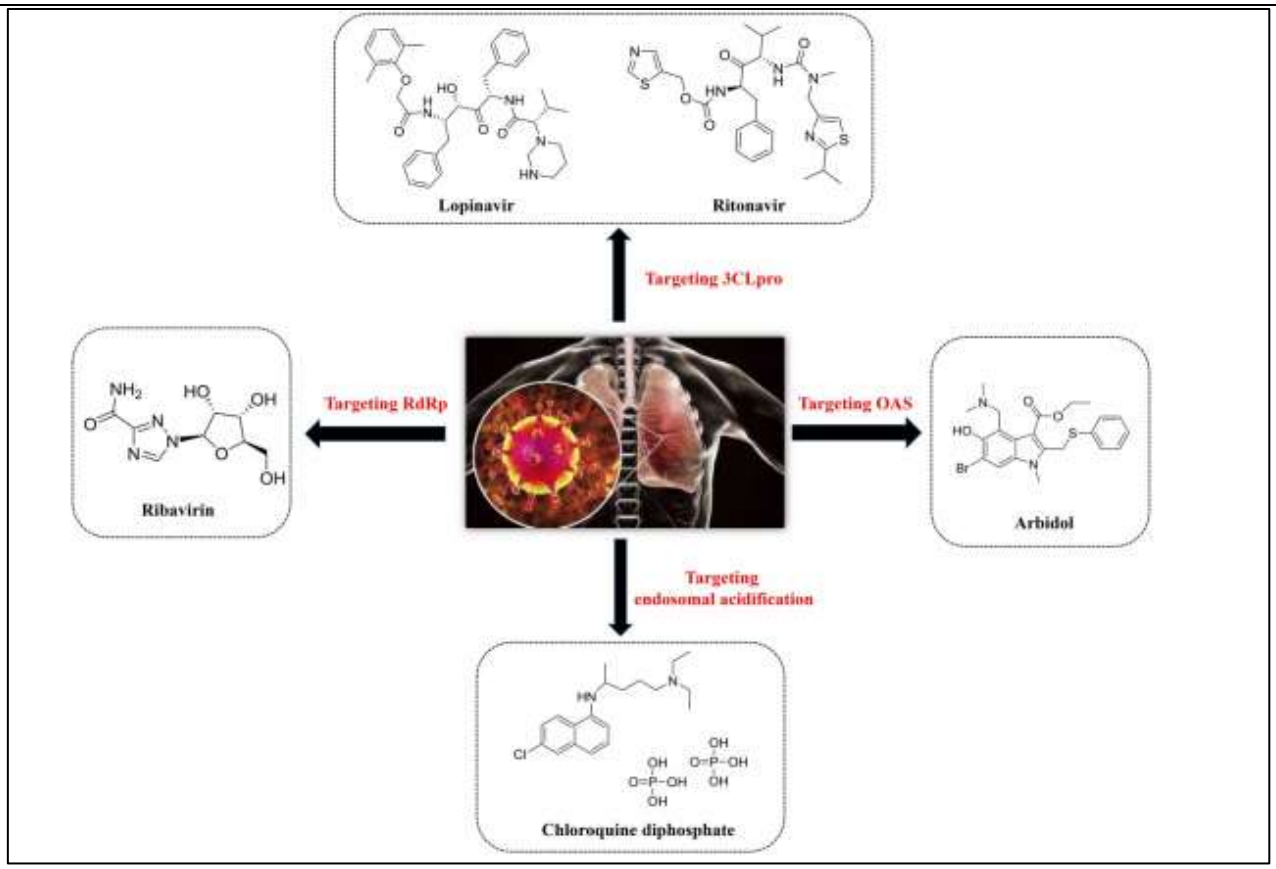

Figure 3. Some kinds of chemicals approved against COVID-19 in China [30].

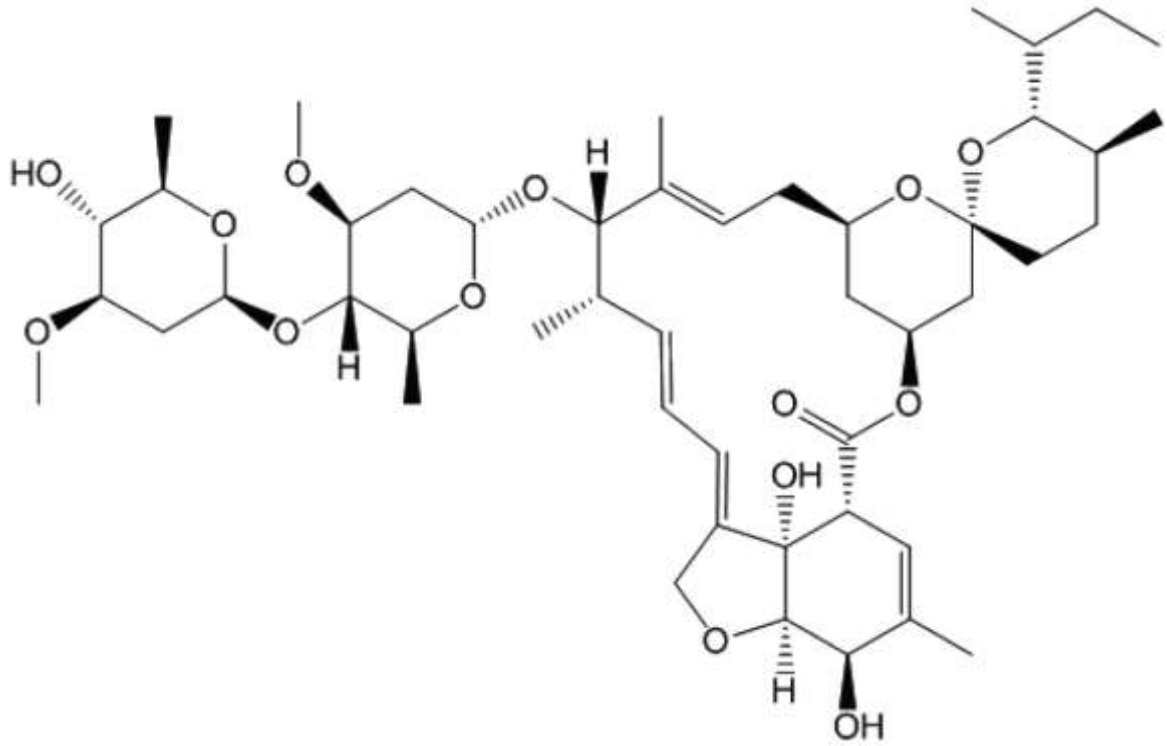

Figure 4. Structure of ivermectin [33].

References

[1] Zhong, N.; Zheng, B.; Li, Y.; Poon, L.; Xie, Z.; Chan, K.; "Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China"; The Lancet. 362, 1353, 2003.

[2] Wang, N.; Shi, X.; Jiang, L.; Zhang, S.; Wang, D.; Tong, P.; "Structure of MERS CoV spike receptor-binding domain complexed with human receptor DPP4"; Cell Res. 23, 986, 2013.

[3] Cui, J.; Li, F.; Shi, Z-L.; "Origin and evolution of pathogenic coronaviruses"; Nat Rev Microbiol. 17, 181–92, 2019.

[4] Lai, C-C.; Shih, T-P.; Ko, W-C.; Tang, H-J.; Hsueh, P-R.; "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID- 19): the epidemic and the challenges"; Int J Antimicrob Agents. 55, 105924, 2020.

[5] Organization, WH.; "Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance"; World Health Organization, 2020.

[6] Aryal, S.; "Structure of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)"; Online Microbiology Notes, January 2020.

[7] Kan, B.; Wang, M.; Jing, H.; Xu, H.; Jiang, X.; Yan, M.; "Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus-like virus in palm civets at an animal market and on farms"; J. Virol. 79, 11892–900, 2005.

[8] Shereen, M.; Khan, S.; Kazmi, A.; Bashir, N.; Siddique, R.; "COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses"; J. Adv. Res. 24, 91–98, 2020.

[9] Luis, A. D.; Hayman, D. T.; O'Shea, T. J.; Cryan, P. M.; Gilbert, A. T.; Pulliam, J. R.; Mills, J. N.; Timonin, M. E.; Willis, C. K.; Cunningham, A. A.; "A comparison of bats and rodents as reservoirs of zoonotic viruses: Are bats special? "; Proc. Biol. Sci. 280, 20122753, 2013.

[10] Anthony, S. J.; Johnson, C. K.; Greig, D. J.; Kramer, S.; Che, X.; Wells, H.; Hicks, A. L.; Joly, D. O.; Wolfe, N. D.; Daszak, P.; "Global patterns in coronavirus diversity"; Virus Evol. 3, 012, 2017.

[11] Davy, C. M.; Donaldson, M. E.; Subudhi, S.; Rapin, N.; Warnecke, L.; Turner, J. M.; Bollinger, T. K.; Kyle, C. J.; Dorville, N. S.; Kunkel, E. L;. "White-nose syndrome is associated with increased replication of a naturally persisting coronaviruses in bats"; Sci. Rep. 8, 15508, 2018.

[12] Letko, M.; Marzi, A.; Munster, V.; "Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses". Nat. Microb. 5, 562–569, 2020.

[13] Zhang, H.; Penninger, J. M.; Li, Y.; Zhong, N; Slutsky, A. S.; "Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target"; Intensive Care Medicine. 46, 586–590, 2020.

[14] Ng, S.; Kasumba, M.; Fujita, T.; Luo, H.; "Spatio-temporal characterization of the antiviral activity of the XRN1-DCP1/2 aggregation against cytoplasmic RNA viruses to prevent cell death"; Cell Death Differ., 1–20, 2020.

[15] Agostini, L.; Andres, L.; Sims, C.; Graham, L.; Sheahan, P.; Lu, X.; "Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease"; Microbio. 9, 221–318, 2018.

[16] Sheahan, P.; Sims, C.; Leist, R.; Schäfer, A.; Won, J.; Brown, J.; "Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV"; Nat. Comm. 11, 1–14, 2020.

[17] Richardson, P.; Griffin, I.; Tucker, C.; Smith, D.; Oechsle, O.; "Phelan, A.; Baricitinib as potential treatment for 2019-nCoV acute respiratory disease"; The Lancet. 395, e30–e31, 2020.

[18] Wu, F.; Zhao, S.; Yu, B.; Chen, M.; Wang, W.; Song, G.; "A new coronavirus associated with human respiratory disease in China"; Nature. 579, 265–269, 2020.

[19] Vincent, J.; Bergeron, E.; Benjannet, S.; Erickson, R.; Rollin, E.; Ksiazek, G.; "Chloroquine is a potent inhibitor of SARS coronavirus infection and spread"; Virol. J. 2, 69, 2005.

[20] Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro"; Cell Res. 30, 269–271, 2020.

[21] Lim, J.; Jeon, S.; Shin, Y.; Kim, J.; Seong, M.; Lee, J.; "Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR"; J. Korean Med. Sci.35, e79, 2020.

[22] Graci, D.; Cameron, E.; "Mechanisms of action of ribavirin against distinct viruses"; Rev. Med. Virol. 16, 37–48, 2006.

[23] "Full Prescribing Information: Arbidol (umifenovir) film-coated tablets 50 and 100 mg: Corrections and Additions". State Register of Medicines (in Russian). Open joint-stock company "Pharmstandard-Tomskchempharm". Retrieved 3 June 2015.

[24] Scavone, C.; Brusco, S.; Bertini, M.; Sportiello, L.; Rafaniello, C.; Zoccoli, A.; "Current pharmacological treatments for COVID-19: what's next?". Bri. J. Pharma., 2020.

[25] Banerjee, A.; Kulcsar, K.; Misra, V.; Frieman, W.; Mossman, K.; "Bats and Coronaviruses"; Viruses. 11, 41, 2019.

[26] Derebail, K.; Falk, J.; "ANCA-associated vasculitis—refining therapy with plasma exchange and glucocorticoids"; Mass Med. Soc. 382, 671–673, 2020.

[27] Tian, X.; Li, C.; Huang, A.; Xia, S.; Lu, S.; Shi, Z.; "Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody"; BioRxiv. 9, 382–385, 2020.

[28] Zhu, H.; Duan, Y.; "Effective Chemicals against Novel Coronavirus (COVID-19) in China"; Cur. Top. Med. Chem. 20, 00, 2020.
[29] "NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19". NIH news releases. Retrieved 5 May 2020.
[30] "EMA starts rolling review of remdesivir for COVID-19". European Medicines Agency (EMA). 30 April 2020. Retrieved 4 May 2020.
[31] Casadevall, A.; Pirofski, L.-A.; "The convalescent sera option for containing COVID-19"; J Clin. Inves. 130, 1545, 2020.
[32] Shen, C.; "Treatment of 5 critically ill patients with COVID-19 with convalescent plasma"; JAMA. 323,1582–1589, 2020.
[33] Del Guidice, P.; Marty, P.; "Ivermectin: A new therapeutic weapon in dermatology? "; Arch. Dermatol., 135,705, 1999.
[34] Turner, J.; Schaeffer, M.; "Mode of action of ivermectin. In: Campbell WC, editor. Ivermectin and Abamectin"; New York: Springer Verlag., 73-88, 1989.
[35] Dent, A.; Davis, W.; "Avery, L.; Avr-15 encodes a chloride channel subunit that mediates inhibitory glutametric neuro transmission and ivermectin sensitivity in Caenorhabditis elegans"; EMBO J. 16, 5867, 1997.
[36] Dourmishev, L.; Dourmishev, A.; Schwartz, A.; "Ivermectin: pharmacology and application in dermatology"; Int. J. Dermatol. 44, 981, 2005.