Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter 9

Dexamethasone: a corticosteroid drug for the treatment of coronavirus disease 2019

Muhammad Riaz[1], Muhammad Akram[2], Chukwuebuka Egbuna[3,4], Ahmed Olatunde[5], Habibu Tijjani[6], Charles Oluwaseun Adetunji[7], Jonathan C. Ifemeje[3], Kingsley C. Patrick-Iwuanyanwu[4,8], Chandan Shivamallu[9], Michael C. Olisah[10], Chukwuemelie Z. Uche[11] and Jude C. Chikwendu[3]

[1]*Department of Allied Health Sciences, Sargodha Medical College, University of Sargodha, Sargodha, Pakistan;* [2]*Department of Eastern Medicine, Government College University Faisalabad, Faisalabad, Punjab, Pakistan;* [3]*Department of Biochemistry, Faculty of Natural Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State, Nigeria;* [4]*Nutritional Biochemistry and Toxicology Unit, World Bank Africa Centre of Excellence, Centre for Public Health and Toxicological Research (ACE-PUTOR), University of Port-Harcourt, Port-Harcourt, Rivers State, Nigeria;* [5]*Department of Medical Biochemistry, Abubakar Tafawa Balewa University, Bauchi, Bauchi State, Nigeria;* [6]*Department of Biochemistry, Natural Products Research Laboratory, Bauchi State University, Gadau, Bauchi State, Nigeria;* [7]*Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo University Iyamho, Auchi, Edo State, Nigeria;* [8]*Department of Biochemistry, Faculty of Science, University of Port Harcourt, Port-Harcourt, Rivers State, Nigeria;* [9]*Department of Biotechnology and Bioinformatics, School of Life Sciences, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India;* [10]*Department of Medical Biochemistry, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State, Nigeria;* [11]*Department of Medical Biochemistry and Molecular Biology, Faculty of Basic Medical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria*

Chapter outline

Coronavirus Drug Discovery. https://doi.org/10.1016/B978-0-323-85156-5.00028-6

9.1 Introduction

The new coronavirus disease 2019 (COVID-19) which emerged from Wuhan, China, is caused by a beta-coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is analogous to the existing severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1−3].

SARS-CoV-2 is a positive-sense, single-stranded, enveloped RNA virus that causes various symptoms of pneumonia such as fatigue, dry cough, fever, difficulty in breathing, myalgia, and others [4]. The human-to-human transmission pattern of SARS-CoV-2 is through contaminated respiratory droplets that contain the virus [5,6]. There are over 600,000 deaths, out of which more than 130,000 COVID-19 cases in the world was of July 2020 [2]. However, no vaccine or antiviral drug is currently available for treating the virus. Hence, it is of utmost importance to come up with treatment strategies as early as possible to curb the outbreak of COVID-19 [7].

Corticosteroids have the potential to inhibit factors of inflammation and are usually co-administered with some antiviral drugs to treat viral pneumonia. Glucocorticoids, an example of corticosteroids, inhibit a variety of pro-inflammatory genes encoding chemokines, cell adhesion molecules, cytokines, receptors, and inflammatory enzymes to restore homeostasis and address altered inflammatory processes [8]. Although the role of corticosteroids remains controversial, satisfactory results are reported from a majority of patients with SARS infection using corticosteroids as a treatment regime [9]. The results of another retrospective study conducted on patients suffering from MERS showed that corticosteroids treated patients likely require vasopressors, renal replacement therapy, and mechanical ventilation [10].

9.2 Pathophysiology of COVID-19

Coronaviruses belong to the respiratory virus family causing various diseases starting from the common cold to MERS and SARS [11], inducing serious extrapulmonary manifestations and lower respiratory tract infections, both of which are of zoonotic origin. SARS-CoV-2 is a relatively new virus and is a member of β-CoV lineage B, first identified by the Chinese Center for Disease Control and Prevention (China CDC) in Wuhan [1]. It has been revealed that the genome sequence of SARS-CoV-2 is 75%−80% identical to that of SARS-CoV with added similarities to some CoVs identified from bats [1]. Epidemiological and clinical features of COVID-19 patients demonstrate that clusters of respiratory illnesses with great resemblance to SARS-CoV in clinical presentation are caused by the SARS-CoV-2 infection, the leading source of admission to the intensive care unit (ICU) with increased mortality [5]. Clinically, the patients suffer from dry cough, fatigue, fever, difficulty in breathing, and acute respiratory distress syndrome (ARDS).

The acute pneumonic process is dominated in COVID-19 pathophysiology as found in extensive radiological opacity on an autopsy including inflammatory infiltrates diffuse alveolar damage, and microvascular thrombosis [12,13]. In the pathophysiology of organ failure, the host immune response plays a vital role in the pathology of organ failure and in other viral pneumonia such as SARS, the highly pathogenic avian influenza, and seasonal and pandemic influenza [14].

In severe COVID-19, injury to inflammatory organs may occur with subsets of patients who have noticeably elevated inflammatory markers like interleukin 1, interleukin 6, ferritin, and C-reactive protein [5,15]. In order to mitigate the injury of inflammatory organs, several therapeutic interventions have been proposed in viral pneumonia, but there is a wide debate about the role of corticosteroids therapy [16].

Most of the COVID-19 infections either result in mild disease or are asymptomatic. Still a considerable fraction of infected people develop illnesses of the respiratory system requiring hospital care and can progress to critical illness having respiratory failure to hypoxia requiring ventilated support for a longer time [17−19].

According to an estimate, about 5% of COVID-19 patients require mechanical ventilation and approximately 14% of the patients needed supplemental oxygen due to the development of respiratory symptoms. Overall, 2.3% case fatality rate was reported by the CDC, which is 49% among the critically ill patients that require mechanical ventilation while higher at 14.8% in older patients more than 80 years of age [20].

In COVID-19, pulmonary pathology is characterized by reactive hyperplasia of pneumocytes with cellular infiltration, patchy inflammation and evidence of intravascular thrombosis, and diffuse alveolar damage. Lymphocytes, macrophages, and monocytes infiltrate the pulmonary interstitium [21]. The infiltration of severe pulmonary inflammation of the pulmonary tissue impedes the exchange of pulmonary gas. In addition, one-fifth of hospitalized patients develop considerable cardiovascular morbidity, characterized by thromboembolic events, tachyarrhythmias, and troponin rise, which is coupled with mortality risk. COVID-19 patients that require hospitalization and intensive care support are presented with clinical symptoms of highly elevated C-reactive protein, lymphopenia, fever, elevated serum ferritin, higher proinflammatory cytokines, and increased D-dimers. In addition, histological examination revealed prominent pulmonary infiltrates with macrophages and monocytes, hypercoagulability, and vasculitis [21].

9.3 Treatment strategies

The rapid increase in SARS-CoV-2 infection worldwide has led to an urgent need for therapeutic intervention or vaccine development to treat or prevent COVID-19 disease. As a result of this, some studies on potential vaccine

candidates or therapeutic interventions are currently in progress [22]. Inflammation is an indispensable component of an effective immune response, and the successful elimination of infections is difficult without the involvement of this physiological process. The inflammatory response starts with the recognition of pathogens followed by the recruitment of immune cells which are capable of eliminating the pathogens and in due course leads to the repair of diseased tissue and restoration of homeostasis. On the other hand, SARS-CoV-2 induces the cytokine storm (prolonged and excessive cytokine/chemokine responses) in some infected individuals [23]. The formed cytokine storm causes multiple organ dysfunction or ARDS leading to physiological deterioration and death. Timely control of cytokine storm in an early stage of the infection by using cytokine antagonists and immunomodulators, as well as reducing the infiltration of lungs inflammatory cells, is crucial in reducing and preventing the mortality rate of COVID-19 patients and to improve the treatment success rate [24]. The mechanism of action of cytokine storm and potential therapy in COVID-19 patients is shown in Fig. 9.1.

9.4 Corticosteroid therapies

Corticosteroids are steroid hormones with potential antiinflammatory functions and are routinely used to suppress inflammation. Corticosteroids are used as the principal immunomodulators during the 2003 SARS epidemic. Their timely administration often results in early improvement like improving oxygenation, relieving the infiltration of radiation in the lungs, and reducing the fever [25]. A retrospective study conducted on 401 severe SARS patients reported that proper glucocorticoids therapy in SARS patients causes a considerable reduction in mortality rate with a marked reduction in the

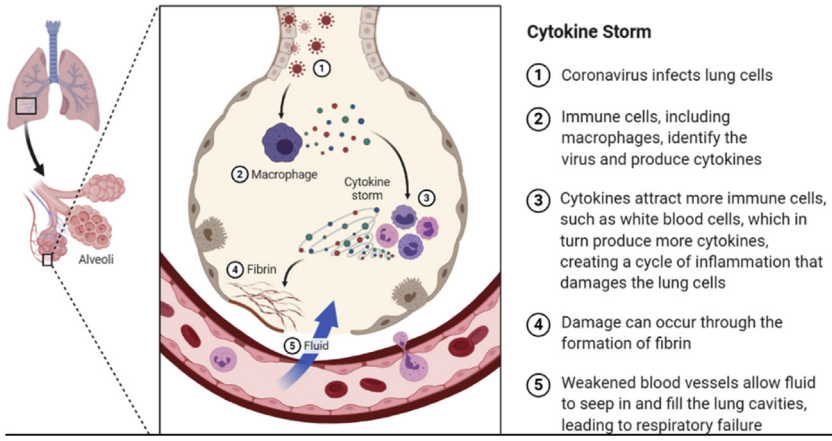

FIGURE 9.1 Mechanism of action of cytokine storm.

hospital stay. Furthermore, glucocorticoid-treated patients are rarely affected with secondary infections and other complications [26]. However, some studies showed that corticosteroid administration during SARS-CoV infection in human-led to adverse consequences. Early corticosteroids treatment of SARS patients resulted in increased viral load in plasma in non-ICU patients leading to disease aggravation. Glucocorticoids use for the treatment of COVID-19 patients has become the main challenge for clinicians [27]. The dose and time of glucocorticoids administration are imperative to the outcome of severely ill patients. Early glucocorticoids therapy inhibits the initiation of defense mechanism of the body, thus increasing the viral load and eventually leading to adverse consequences. Hence, the use of glucocorticoids is mainly limited to patients who are critically ill and suffering from inflammatory cytokine storm. The timely glucocorticoids administration during the early stage of inflammatory cytokine storm inhibits excessive inflammation, thereby effectively preventing the occurrence of ARDS and protecting the functional capacity of the patients' organs. The short-term (2−3 days) use of glucocorticoids is appropriate with the recommended dose of no greater than 1−2 mg/kg/day methylprednisolone equivalent in patients with excessive inflammatory response, rapid imaging progress, and progressive deterioration of oxygenation indicators [18]. It is noteworthy that glucocorticoids in large doses may delay the coronavirus clearance due to immunosuppression.

9.5 Role of dexamethasone in COVID-19 treatment

One of the major mysteries in the treatment of COVID-19 patients is the recurrent formation of blood clots consequently damaging the organs of the patient and occasionally being fatal. New findings by researchers from Yale Cancer Center (YCC) and experts from several medical specialities at Yale pinpoint a biological marker that helps in treating COVID-19 patients and identifying the leading mechanism following the pathophysiology of COVID-19. The study was published in the Lancet Haematology [28].

Dexamethasone (Fig. 9.2) is a routinely used steroid, which is inexpensive and can save the lives of people seriously ill with COVID-19. A randomized, controlled clinical trial conducted in the United Kingdom has found that dexamethasone is the first drug shown to decrease deaths from the coronavirus that has killed more than 600,000 people globally. The results of the trial showed that it reduces the deaths to nearly one-third in coronavirus patients who were on ventilators [29].

Therefore, corticosteroids have the potential to inhibit inflammatory factors and are routinely used as treatment supplements for viral pneumonia. Corticosteroids such as glucocorticoids exert their antiinflammatory potential by inhibiting a large number of proinflammatory genes encoding chemokines, cytokines, inflammatory enzymes, receptors, and the cell adhesion molecules to restore homeostasis and address the inflammatory processes [30].

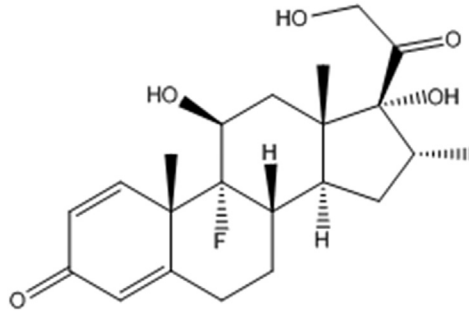

FIGURE 9.2 Chemical structure of dexamethasone.

9.5.1 Case studies

In 2020, So et al. [31] reported a case series of seven mechanically ventilated patients with ARDS caused by COVID-19 who received early treatment with high-dose, short-term systemic corticosteroids to prevent the overproduction of cytokine. Four out of seven patients were male with 69 years median age. The patients were intubated for 7 days following admission at that time with rapidly worsened respiratory status. The patients were treated by administering 1000 or 500 mg/day intravenous methylprednisolone followed by the administration of 1 mg/kg and tapered off. The total corticosteroids administration lasts for a median duration of 13 days. This short-term, high-dose corticosteroid therapy enabled the patients to extubate within 7 days. Still, the data on corticosteroid therapy as the treatment of choice is mixed and many questions on COVID-19 patients' clinical management remain unanswered.

Horby and his colleagues [32] studied the efficacy of dexamethasone in randomly allocated 2104 patients. The results were compared with concurrently allocated 4321 patients with usual care. Overall, the patients died within 28 days included 454 (21.6%) patients treated with dexamethasone and 1065 (24.6%) patients allocated the usual care (95% confidence interval [CI] 0.74 to 0.92; age-adjusted rate ratio [RR] 0.83; $P < .001$). Reduction in the absolute and proportional mortality rate varied significantly and is dependent on the level of respiratory support at randomization. The death of patients on invasive mechanical ventilation was reduced to one-third by dexamethasone (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51−0.82]; $P < .001$), while one-fifth in patients without mechanical ventilation and receiving oxygen (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70−0.92]; $P = .002$), but the mortality rate was not reduced in patients without respiratory support (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93−1.61]; $P = .14$) [32].

Villar et al. [33] reported in their study conducted on patients with severe ARDS in March 28, 2013 to December 31, 2018, that dexamethasone administration could reduce the time of mechanical ventilation and overall mortality in severe ARDS patients.

Earlier studies revealed that extensive lung damage and pulmonary inflammation in infected patients with MERS-CoV and SARS-CoV were associated with increased proinflammatory cytokines [24].

ARDS increased the death risk and there are chances of deaths in the nonsurvivors within 1−2 weeks of ICU admission. In view of increased cytokines during SARS-CoV-2, MERS-CoV, and SARS-CoV infections, severe illness has been usually treated with corticosteroids, for the possible benefit of reducing the lung injury induced by inflammation [30].

On the other hand, current evidence in MERS and SARS patients suggests no effect of corticosteroids on mortality, rather delayed the clearance of viruses [10]. Hence, COVID-19 patients should not be routinely treated with glucocorticoids, unless evidence-based is conducted while monitoring adrenal insufficiency, refractory septic shock, and chronic obstructive lung disease exacerbation or asthma [20]. However, glucocorticoids administration in critically ill, ARDS-associated COVID-19 patients is controversial. Moreover, clinicians noted that dexamethasone administration in early stage of the disease could reduce the overall mortality in severe ARDS patients and the duration of mechanical ventilation [33].

It was hypothesized in a study that corticosteroids therapy in high doses can prevent tissue damage and thus help to mitigate the extent of lung injury. They started corticosteroid therapy in high doses during early respiratory failure prior to the progression of pneumonia virus-related ARDS. Published reports indicated that for the treatment of SARS and MERS, corticosteroid therapy could damage and worsen the patient prognosis [34]. The patients have been limited to short-term regimens. Intravenous methylprednisolone reduced the fever in patients leading to the weaning from mechanical ventilation, resulting in 100% survival rate with 0% reintubation rate, followed by the absolute removal of ventilator support within 7 days in all cases. That case series finding suggested that short-term, high-dose corticosteroid therapy in COVID-19−related ARDS patients provides a good prognosis without any critical side effects. The study had limited number of cases and contained the single center report. Findings of the case series urged the need of more studies to elucidate the potential of corticosteroid therapy in COVID-19 [10].

Dexamethasone (6 mg/day) treatment for 10 days in COVID-19 patients undergoing respiratory support reduced the 28-day mortality. Based on these findings, one death would be barred by the treatment of 40 patients without mechanical ventilation, or around 25 patients requiring oxygen or around 8 patients requiring invasive mechanical ventilation [33]. Before completing this trial, various guidelines for the treatment of COVID-19 patients have stated that the use of corticosteroids is either not recommended or contraindicated in

COVID-19 [35]. Updated reports should be followed as has already happened in the United Kingdom. The most effective treatment for critically ill COVID-19 patients is dexamethasone, and being inexpensive, safe, and wide availability, it is the one that can be used worldwide [36].

9.6 Future projections

From the foregoing, it could be understood that the pathobiology of SARS-CoV-2 is associated to ARDS which is caused by autoimmune destruction of lung cells originating through the release of proinflammatory cytokines in what is called cytokine storm. Measures to reduce the release of cytokines have proved useful and could be a guide toward the discovery of new and effective drugs.

In light of the recent trends, authors recommend that the cautious use of antiinflammatory agents, taking note of the patient medical history, should be supported by other drugs especially those capable of boosting the immune system. Suppressing the efforts of the SARS-CoV-2 in invading healthy cells of the body could be a viable treatment option than spending tens of thousands of dollars developing a "miracle" drug while lives are lost.

Again, the authors recommended that efforts should be directed to natural products especially medicinal plants with potent antiviral, immunomodulating, and anti-inflammatory properties. Many collections of Egbuna and his collaborating team have presented the sources for these compounds in their books and book chapters [37–45].

9.7 Conclusion

The outbreak of COVID-19 that emerged from Wuhan, China, in December 2019 with links to zoonotic sources is known to be caused by SARS-CoV-2, which share similarities to SARS and MERS. The rate at which it spreads and the number of deaths recorded show that it is the greatest threat to mankind in modern history. There is currently no drug or vaccine with express approval to treat COVID-19. However, some immune-modulating drugs and antiviral agents are on trial. Recently, it has been indicated that the corticosteroid drug, dexamethasone, may have the potential to reduce the mortality of patients suffering from severe COVID-19.

List abbreviations

ARDS Acute respiratory distress syndrome
China CDC Chinese Center for Disease Control and Prevention
COVID-19 Coronavirus disease 2019
ICU Intensive care unit
MERS-CoV Middle East respiratory syndrome coronavirus
RNA Ribonucleic acid

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
WHO World Health Organization
β-CoV Beta-coronavirus

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727−33. https://doi.org/10.1056/NEJMoa2001017.

[2] Gorbalenya AE, Baker SC, Baric R, Groot RJD, Drosten C, Gulyaeva AA, Penzar D. Severe acute respiratory syndrome-related coronavirus: the species and its viruses−a statement of the Coronavirus Study Group. Nat Microbiol 2020;5:536−44.

[3] WHO. WHO Director-General's opening remarks at the mission briefing on COVID-19 -. March 19, 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-openingremarks-at-the-mission-briefing-on-covid-19. [Accessed 18 July 2020].

[4] He F, Deng Y, Li W. Coronavirus disease 2019: what we know? J Med Virol 2020;92(7):719−25.

[5] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497−506.

[6] Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, Tsoi HW. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395(10223):514−23.

[7] Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020;14(1):69−71.

[8] Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti-and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation 2015;22(1−2):20−32.

[9] Yam LYC, Lau ACW, Lai FYL, Shung E, Chan J, Wong V, Hong Kong Hospital Authority SARS Collaborative Group (HASCOG). Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. J Infect 2007;54(1):28−39.

[10] Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med 2018;197(6):757−67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161116.

[11] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Zhang X. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130(5):2620−9. https://doi.org/10.1172/JCI137244.

[12] Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, Marcia Negri E. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemostasis 2020;18(6):1517−9.

[13] Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, Galli M. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 2020:1−6. https://doi.org/10.1016/S1473-3099(20)30434-5.

[14] Baillie JK, Digard P. Influenza—time to target the host? N Engl J Med 2013;369(2):191−3.

[15] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020;368(6490):473−4.

[16] Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395(10225):683.

[17] Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis, vol. 20; 2020. p. 669–77.
[18] Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, Cao B. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Chin J Tuber & Respir Dis 2020;43(3):183–4.
[19] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intens Care Med 2020;46(5):846–8.
[20] World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020 (No. WHO/2019-nCoV/clinical/2020.4). World Health Organization; 2020.
[21] Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020;15(5):700–4.
[22] Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, et al. COVID-19: a promising cure for the global panic. Sci Total Environ 2020;725(138277):1–18.
[23] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the Cytokine Storm'in COVID-19. J Infect 2020;80(6):607–13.
[24] Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 2018;104:8–13.
[25] Auyeung TW, Lee JS, Lai WK, Choi CH, Lee HK, Lee JS, Yeung YM. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005;51(2):98–102.
[26] Chen RC, Tang XP, Tan SY, Liang BL, Wan ZY, Fang JQ, Zhong N. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest 2006;129(6):1441–52.
[27] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Chen HD. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.
[28] Goshua G, Pine AB, Meizlish ML, Chang C-H, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. The Lancet Hematol 2020;7(8):575–82. https://doi.org/10.1016/S2352-3026(20)30216-7.
[29] Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature 2020;582(7813). 469-469.
[30] Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect 2020;81(1):e13–20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32283144.
[31] So C, Ro S, Murakami M, Imai R, Jinta T. High-dose, short-term corticosteroids for ARDS caused by COVID-19: a case series. Respirol Case Rep 2020;8(6):e00596.
[32] Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, Prudon B. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. MedRxiv 2020. https://doi.org/10.1101/2020.06.22.20137273. Preprint.
[33] Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, Martín-Rodríguez C. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020;8(3):267–76.

[34] Peiris JSM, Chu CM, Cheng VCC, Chan KS, Hung IFN, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361(9371):1767–72.

[35] Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancer 2020;14(1023):1–3. https://doi.org/10.3332/ecancer.2020.1023. www.ecancer.org.

[36] Mahase E. Covid-19: what treatments are being investigated? BMJ 2020;368. https://doi.org/10.1136/bmj.m1252.

[37] Kaliyaperumal S, Periyasamy K, Balakrishnan U, Palanivel P, Egbuna C. Antiviral phytocompounds for drug development: a data mining studies. In: Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Saravanan K, editors. Phytochemicals as lead compounds for new drug discovery. USA: Elsevier; 2019, ISBN 9780128178911.

[38] Nwosu O, Keskin M, Lohani H, Egbuna C, Haider SZ. Bioactive lead compounds and molecular targets for the development of anti-inflammatory drugs. In: Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Saravanan K, editors. Phytochemicals as lead compounds for new drug discovery. USA: Elsevier; 2019, ISBN 9780128178911.

[39] Singh p, Gupta E, Mishra N, Mishra P. Shikimic acid as intermediary model for the production of drugs effective against influenza virus. In: Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Saravanan K, editors. Phytochemicals as lead compounds for new drug discovery. USA: Elsevier; 2019, ISBN 9780128178911.

[40] Egbuna C, Kumar S, Ezzat SM, Ifemeje JC, Saravanan K, editors. Phytochemicals as lead compounds for new drug discovery. USA: Elsevier; 2019, ISBN 9780128178911. https://www.elsevier.com/books/phytochemicals-as-lead-compounds-for-new-drug-discovery/egbuna/978-0-12-817890-4.

[41] Ezzat SM, Jeevanandam J, Egbuna C, Kumar S, Ifemeje JC. Phytochemicals as sources of drugs. In: Kumar S, Egbuna C, editors. Phytochemistry: in vitro and in silico updates. Singapore: Springer Nature; 2019. p. 3–22.

[42] Srivastav VK, Egbuna C, Tiwari M. Plant secondary metabolites as lead compounds for the production of potent drugs. In: Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Saravanan K, editors. Phytochemicals as lead compounds for new drug discovery. USA: Elsevier; 2019, ISBN 9780128178911.

[43] Egbuna C, Ifemeje JC, Udedi SC, Kumar S, editors. Phytochemistry. Fundamentals, methods, and applications, vol. 1. New York: Apple Academic Press; 2018, ISBN 978-1771887595. p. 684. Part of a 3 volume set.

[44] Egbuna C, Kumar S, Ifemeje JC, Kurhekar JV, editors. Phytochemistry. Pharmacognosy, nanomedicine, and contemporary issues, vol. 2. New York: Apple Academic Press; 2018, ISBN 978-1771887601. p. 620. Part of a 3 volume set.

[45] Egbuna C, Ifemeje JC, Kumar S, Sharif N, editors. Phytochemistry. Marine, industrial, and advances, vol. 3. New York: Apple Academic Press; 2018, ISBN 978-1771887618. p. 502. Part of a 3 volume set.