

Dexamethasone an Old Medicine for Covid-19

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1.0 General Introduction

1.1 What is Covid-19?

According to xxxxxxxx (WHO), Coronavirus disease 2019 (Covid-19) is a transmittable illness triggered by a novel coronavirus. Formally the virus was referred to as 2019-CoV. Currently, the disease is referred to as a severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2).¹ The virus was first identified upon the outbreak and respiratory illness in Wuhan City, Hubei Province, China. However, Covid-19 was first reported to WHO on December 31, 2019.² WHO then confirmed Covid-19 a worldwide health emergency on January 30, 2020.³ The disease was declared a universal pandemic on March 11, 2020.

Individuals diagnosed with Covid-19 experiences mild to moderate breathing disease and may recuperate without significant management. However, older persons and individuals with primary medical conditions such as chronic respiratory disease, diabetes, cancer, and cardiovascular illnesses are more likely to develop severe symptoms of Covid-19.⁴ According to WHO, the most appropriate way to prevent Covid-19 from spreading is to wash hands with running water or using an alcohol-based rub frequently.⁵ WHO advises people to avoid touching their face. The Covid-19 spreads via droplets of saliva or discharges from the nose when ill individual coughs or sneezes. WHO advises people to observe breathing etiquette, such as coughing into a flexed elbow.

¹ Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). *Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein*. *Cell*. P 1.

² Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., ... & Agha, R. (2020). World Health Organization declares global emergency A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*. P. 4

³ Ibid.

⁴ Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). *Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein*. *Cell*. P 3.

⁵ Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., ... & Agha, R. (2020). World Health Organization declares global emergency A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*. P. 5

Origin of Covid-19

Health officials in China and WHO suspect a Market in Wuhan, China that sold both dead and live animals as the origin of Covid-19. According to Cui, Li & Shi (2019),⁶ Covid-19 is a Middle East respiratory syndrome coronavirus (MERS-CoV) that originates from bats. Genetically diverse coronavirus are linked to MERS-CoV and SARS-CoV and was discovered in bats worldwide.

Types of Coronaviruses

A virus is a microscopic parasite, which is unable to reproduce by itself. Upon infecting a susceptible cell, the virus directs cell machinery to produce more virus. Most viruses contain deoxyribonucleic acid (DNA) or Ribonucleic acid (RNA) as genetic materials. Additionally, the nucleic acid of a virus may be either double-stranded or single.⁷ All the infectious virus particles called a virion have nucleic acid and an outer shell of protein. On the virus structure, a virus has two main components, the protein capsid, which covers the genome and a nucleic acid genome. The nucleic acid genome and protein capsid are both called a nucleocapsid.⁸ Many viruses also contain lipid envelope. Hence as earlier mentioned, the entire structure is the virion. The word “Corona” is a Latin word meaning “crown” and it may refer to the SARS-CoV-2, which is the coronavirus, which is responsible for 2019, and 2020 outbreak. The work also refers to the coronavirus disease 2019 (COVID-19), which is the disease that causes the virus. Therefore, coronavirus is classified based on the crown or halo-like appearance of the envelope glycoproteins.

⁶ Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology*, 17(3), 181

⁷ Lodish, Harvey, Arnold Berk, S. Lawrence Zipursky, Paul Matsudaira, David Baltimore, and James Darnell. "Viruses: Structure, function, and uses." In *Molecular Cell Biology*. 4th edition. WH Freeman, 2000.

⁸ Ibid.

Classification is equally based on the characteristic feature of chemistry and replication⁹. Thus, human coronavirus falls into two serotypes, 229E-like and OC43-like.

Several coronaviruses exist. However, only seven coronavirus affects humans. Four coronaviruses like 229E, HKU1, NL63, and OC42 cause mild or flue like symptoms. Three coronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2, poses a serious health risk to humans. (Figure 1). The virus 229E denotes a coronavirus that affects both bats and humans.¹⁰ The 229E is enveloped, single-stranded RNA, and Positive-sense virus (this a virus that uses a positive sense single stranded RNA as part of its genetic material) attacks the host by binding to the APN receptor. Both OC43 and 229E are known to be responsible for common cold. NL63, on the other hand, is a special type of coronavirus, a setracovirus originating from the Alphacoronavirus genus. The NL63 was identified in Netherlands in late 2004 upon the attack of a seven-month-old child with bronchitis. The OC43, on the other hand, is a member of the species Betacoronavirus 1 and affects both cattle and humans. Regarding the OC43, the virus is an encased positive, single-strained RNA virus that attacks the body by binding to the N-acetyl-9-O-acetylneuraminic acid receptor.¹¹ The HKU1 originated from infected mice. The HKU1, attacks the upper respiratory organs and has symptoms such as a common cold but can proceed to be bronchitis and pneumonia. Hong Kong became the first location of HKU1 in 2005.

⁹ Tyrrell, D. A. J., and S. H. Myint. "Chapter 60: Coronaviruses."

¹⁰ Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*

¹¹ Sohrabi, Catrin, Zaid Alsafi, Niamh O'Neill, Mehdi Khan, Ahmed Kerwan, Ahmed Al-Jabir, Christos Iosifidis, and Riaz Agha. "World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19)." *International Journal of Surgery* (2020).

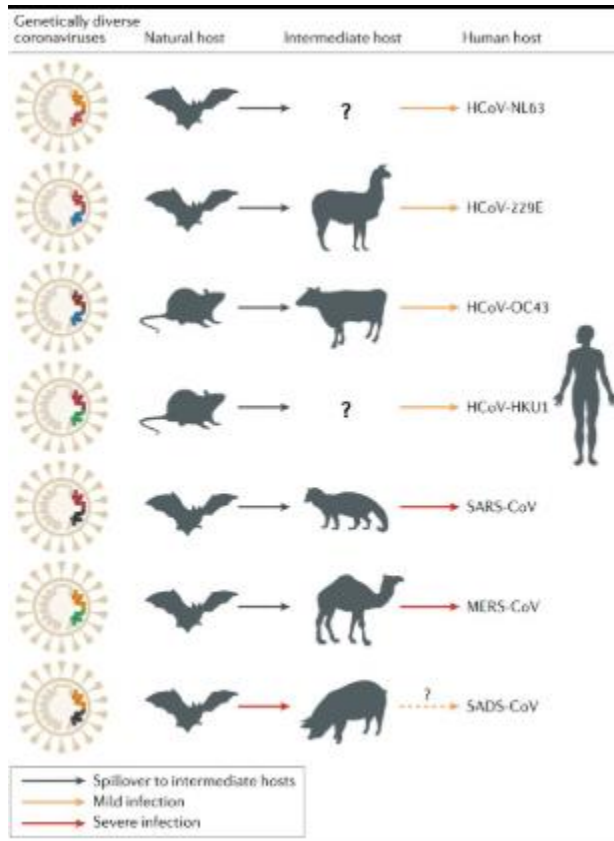


Figure 1: Animal Origins of Human Coronaviruses

Source: <https://www.nature.com/articles/s41579-018-0118-9>

SARS-CoV: The disease, according to WHO, was first recorded in China in 2002. SARS-CoV may have originated in bats but were transmitted to other animals before attacking humans.¹² Between 2002 and 2003 SARS-CoV, more than 8000 people were infected in 26 countries worldwide.

MERS-CoV: According to the WHO, MERS-CoV emerged in Saudi Arabia in September 2012, but its first cases were traced to Jordan. Contact with infected camels led to the contraction

¹² Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*

of the MERS-CoV by humans.¹³ MERS-CoV led to 2400 cases. MERS-CoV appeared again in South Korea in 2015, infecting 186 people leading to 36 deaths.

SARS-Cov-2: according to WHO, the SARS-Cov-2 causes Covid-19. The virus was first reported in Wuhan upon acknowledging an increase in pneumonia cases with no known cause. The cases of Covid-19 have been linked to the market selling poultry and seafood.¹⁴ Even if the virus is likely to have evolved from the animals, the exact source is unknown. SARS-CoV-2 is more dangerous since it is easily transmitted from infected individuals to uninfected people irrespective of the virus's signs and indicators. Walls et al. (2020) provides that the coronavirus's entry into the host be facilitated by the transmembrane spike (s) glycoprotein that forms bulging forms on the viral exterior. S contains two functional subunits that facilitate binding to the cells receptor (S1 Subunits) and the others responsible for fusion of the virus and cellular membrane denoted by S2 Subunits. Thus, SARS-CoV-2 uses the Angiotensin-converting enzyme 2 (ACE2) to enter the cells.¹⁵ The ACE2 as an enzyme attached to the cell membrane of a cell in various body organs like intestine, kidney, heart and lungs, lowers the blood pressure though catalyzing the hydrolysis of angiotensin II into angiotensin. Additionally, counters the activities of similar angiotensin-converting enzyme through reduction of amount of angiotensin II while increasing the Angiotensin. The reduction of angiotensin II make the cell a promising drug target towards treatment of cardiovascular disease. SARS-CoV and SARS-CoV binds to the cells with similar affinities to ACE2.

¹³ Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*

¹⁴ Sohrabi, Catrin, Zaid Alsafi, Niamh O'Neill, Mehdi Khan, Ahmed Kerwan, Ahmed Al-Jabir, Christos Iosifidis, and Riaz Agha. "World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19)." *International Journal of Surgery* (2020)

¹⁵ Kuba, K., Imai, Y., Rao, S. et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* **11**, 875–879 (2005).

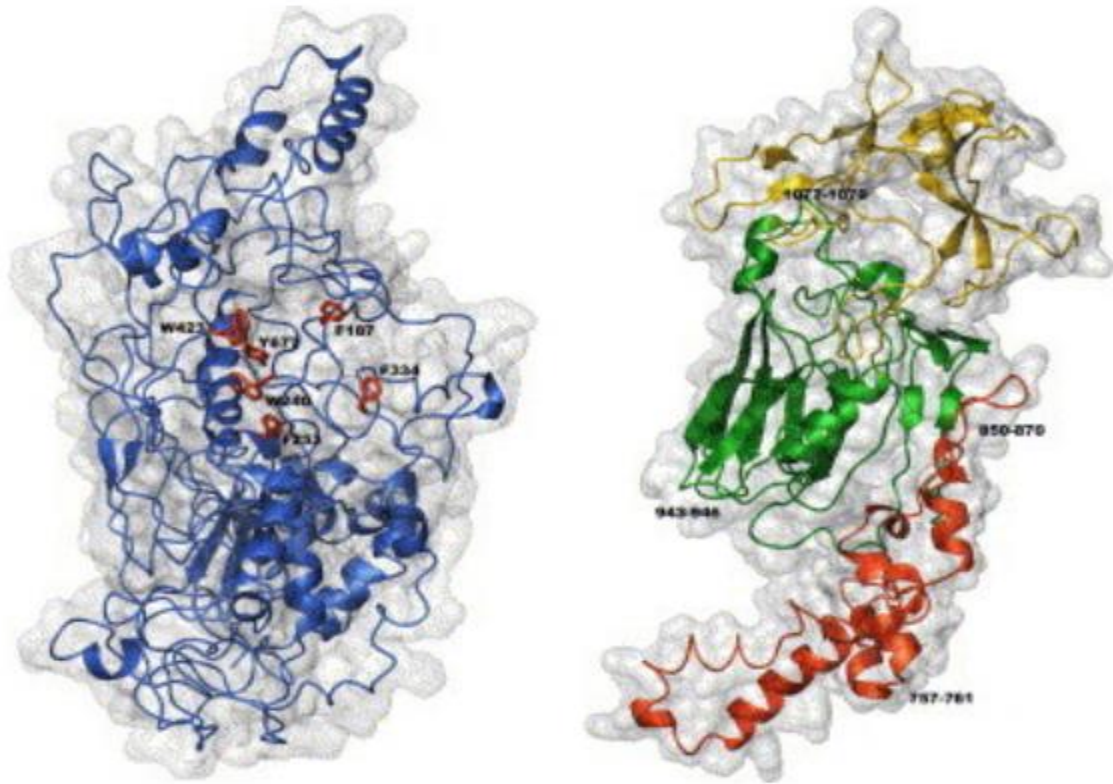


Figure 2a: Surface and ribbon illustrations of tertiary structure of the S1 and S2 subunits of SARS_CoV S glycoprotein

Source: (Spiga et al., 2003)

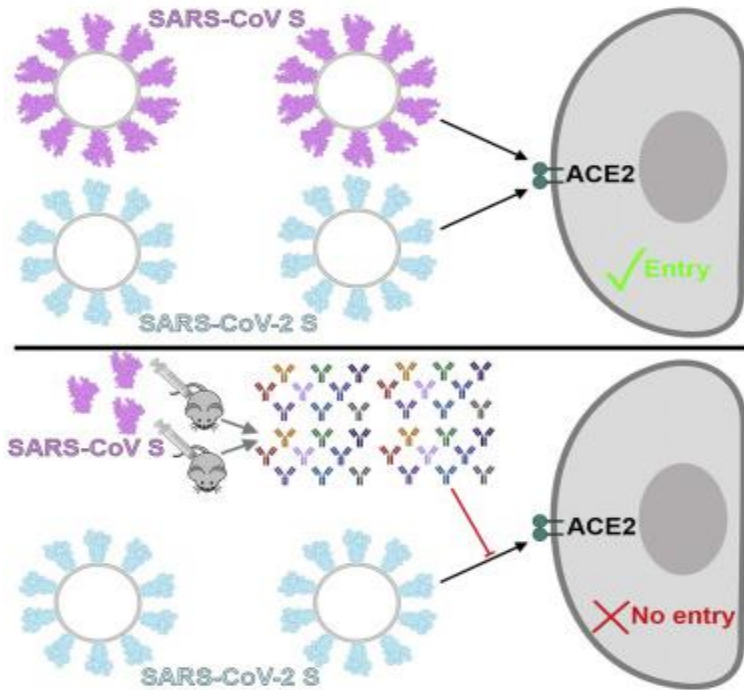


Figure 2b: SARS-CoV-2 attacking cells

Source: Walls et al. (2020)

1.2 Significance of Covid-19

As of June 12, 2020, the World Health Organization (WHO) indicated that over 7.2 million people were infected with Covid-19, and 413,372 deaths had occurred.¹⁶ As an active pandemic, Covid-19 continues to spread. The world economy is at its lowest, with unemployment rising to 5.3 million globally and major economies expected to lose up to 2.4 percent of their GDP.¹⁷ Most of countries are under lockdown across the globe. According to WHO, as of June 12, 2020, no vaccine has been identified to satisfactorily treat Covid-19. Scientists on Covid-19 met WHO between 11 and 12 February 2020 to evaluate the new information on the virus.

Many studies, including Duffy (2018), provides that viruses mutate continually, making it hard to develop a single cure for viral diseases like Covid-19. Nearly a quarter of common flues are due to human coronaviruses. Nonetheless, the immune response diminishes so rapidly that reinfection is bound to occur. A team at Oxford University analyzed recovered Covid-19 patients and established that the strengths of Immunoglobulin G antibodies answerable for longer-lasting immunity, are only high in the first month of viral attack, but begin to drop after that. The IgG is a type of antibody responsible for about 75% of the serum antibodies in humans. Thus, IgG is the most common type of antibody in human blood circulation.¹⁸ Also, the genetic stability of the virus equally matters. Hence, the IgG antibody test seeks to establish the antibodies that work against the virus that causes Covid-19. Thus, some viruses like HIV, influenza, and other viruses transform so rapidly that finding a vaccine becomes a problem. For instance, the virus change in phenotype or growth caused by introduction of inheritable materials.

¹⁶ Sohrabi, Catrin, Zaid Alsafi, Niamh O'Neill, Mehdi Khan, Ahmed Kerwan, Ahmed Al-Jabir, Christos Iosifidis, and Riaz Agha. "World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19)." *International Journal of Surgery* (2020)

¹⁷ Eurosurveillance Editorial Team. (2020). Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. *Eurosurveillance*, 25(5)

¹⁸ *Ibid.*

The WHO and scientists across the globe continue to build on recent outbreaks such as MERS-CoV, Ebola, and SARS-CoV to support the R&D on the Covid-19, but success is yet to come. Every country across the world continues to focus on the possible vaccines with both little and major success realized. Major economies like the US, UK, and Italy, are some of the worst hit countries with the pandemic and have invested heavily in the R&D on Covid-19. Therefore, the most important question to pursue would be **“Why is dexamethasone, an old medicine proving to be the only effective treatment for Covid-19?”** Therefore, to provide an answer to the research question, we will review the chemistry and biological activity of this medicine, and its potency against Covid-19.

2.0 The Chemistry Dexamethasone

2.1 Introduction to Steroids

Steroids define a group of lipophilic compounds that are derived from a variety of marine, synthetic and terrestrial sources. On the other hand, De Nicola & Deniselle (2019)¹⁹ defines steroids as either synthetics or natural organic compounds categorized by molecular assembly of carbon atoms organized in four rings. Steroid groups consist of all the bile acids, sterols of vertebrates, sex hormones, molting hormone in insects, and adrenal cortical homes. Steroids, including their metabolites, partake a significant roles in the biochemistry and psychology of living things from which they are isolated. Several synthetics steroids are used broadly as anti-hormones drugs, anti-inflammatories, and anti-asthmatics, anesthetics and antibiotics.

As earlier highlighted, the core structure of steroids contains seventeen atoms and bounded with four rings. The rings A, B, and C, are the three six-membered cyclohexane rings and ring D is the fused cyclopentane ring, as represented by cholestanol (Figure 1).

¹⁹ De Nicola, A. F., & Deniselle, M. C. G. (2019). Introduction to the Special Issue “Neuroactive Steroids”.

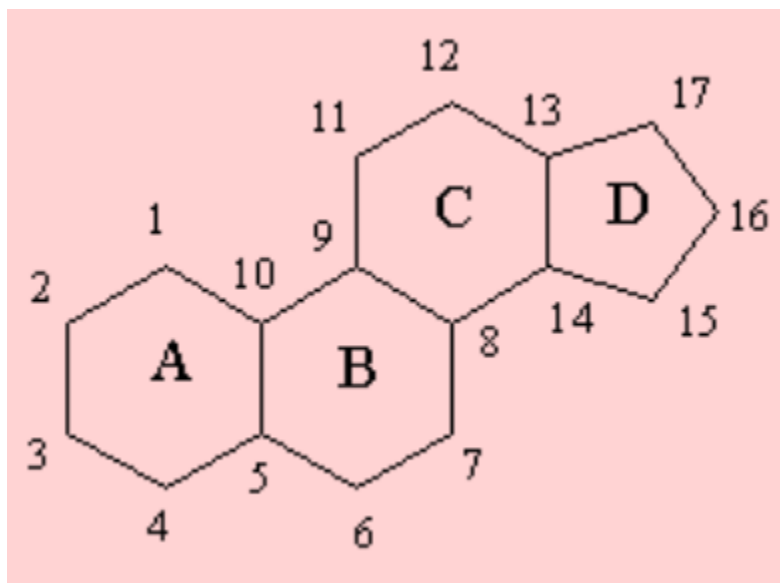


Figure 1. Cholestanol

Source: <http://www.chm.bris.ac.uk/motm/THG/THGh.htm>

Steroid classification

The four-ring gonane structure is common to all the steroids, and it permits different substitutes to be a parent at various positions, making the classification of steroids quite complex. As of the 1950s, biochemists such as Percy Julian begun to classify steroids based only on the number of carbon atoms on the commonly linked substituents on the Sterene (Alhazzani et al. (2020). Thus, under this classification, five major steroids division were identified. Pregnanes (with 21 carbons), cholestanes (with 27 carbons), estranes (with 18 carbons), cholestanes (with 27 carbons), and cholic acid (with 24 carbons) (Walls et al. 2020). Nevertheless, the broader steroid classification was performed based on the number of nuclear carbons and side-chain or functional groups present at C-17. The classification led to the formation of Spirostan (27 carbons), Bufanolide (24 carbons), Cardanolide (23 carbons), Lanostane (27, 30-32 carbons), Stigmastane (29 carbons), Ergostane (28 carbons), Cholestane (27 carbons), Cholane (24 carbons) and Pregnane (21 carbons).

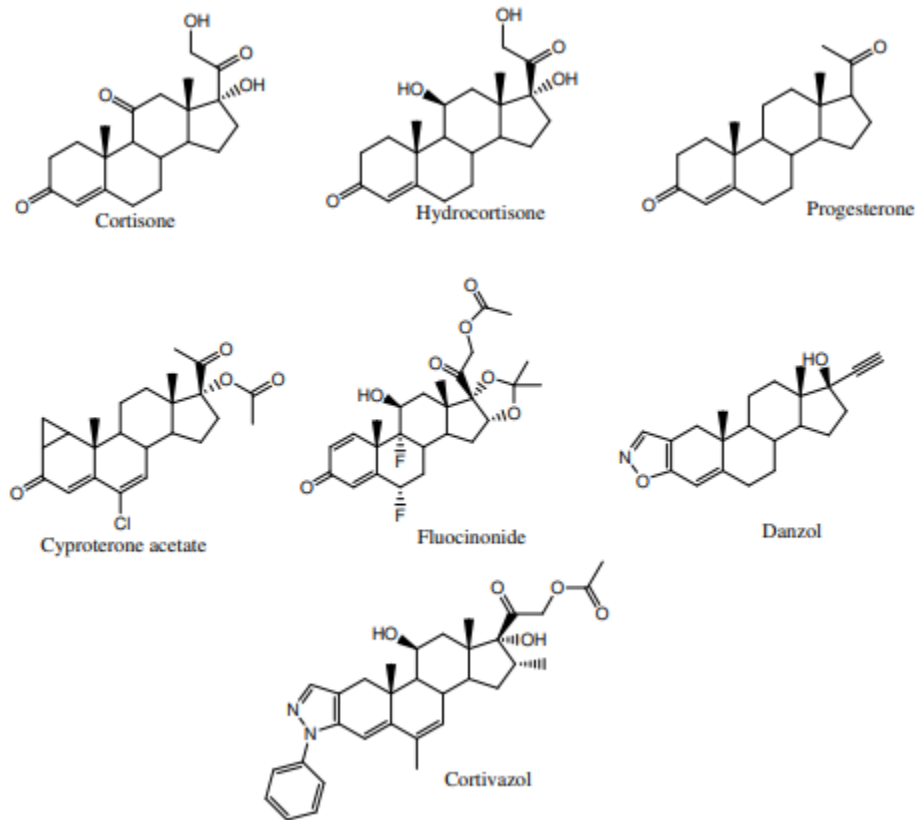


Figure 4a: Examples of Pregnanes

Steroids can also be classified on the nature of steroids. Tablets, liquid, and syrup is one classification with an example as prednisolone. The inhalers and nasal spray steroids include beclometasone and fluticasone. Injection steroids are steroids administered through blood vessels, muscles, or joints, and methylprednisolone is an example.²⁰ Creams, gels, and lotions steroids may include Hydrocortisone skin creams. Steroids may equally affect some medical conditions like blood pressure problems, diabetes, heart problems, or mental health issues.

Side effects of steroids: steroids do not cause major side effects if taken for a short period or at a lower dose. However, steroids may cause unpleasant side effects like mood change, loss of

²⁰ Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*

appetite, and insomnia.²¹ The side effect often passes if the patient completes treatments. If potentials have an infection or any wound, steroids should not be prescribed as they may delay the recovery of the symptoms. Hence, the doctors must make sure that the administered steroids do not make the stated conditions worse.

2.2 Synthesis and Manufacture of Dexamethasone

Dexamethasone is an oral tablet available in the market both as a generic and brand-name drug. The brand name is DexPak. The drug comes as eye drops, ear drops, oral tablets, or oral solutions. Dexamethasone can also be an injectable solution or in an intraocular solution administered after surgery.²² The drug is used in the treatment of several conditions. The conditions may include flare-ups of ulcerative colitis, allergic reactions, and inflammation. The admission can equally treat adrenal insufficiency of dexamethasone.

Chemistry of manufacture of Dexamethasone: Research by Parikh et al. (2015)²³ reveal that dexamethasone is developed in a complex course as obtained from the 3α -acetoxy-16-pregnen-11,20-dione that is further reacted with methyl-magnesium bromide in the company of lithium bromide to produce 3α -hydroxy-16 α -methylpregnan-11,20-dione and thereafter a 17α -hydroxyl group is added. The reaction is further facilitated by acetic anhydride (one of the most simplest acid hydrides and a commonly used reagent during an organic synthesis) in the presence of a *p*-toluenesulfonic acid.²⁴ The end reaction is the 3-acetoxy-17-enolacetate 27.1.40, and reacted with a resin, perbenzoic acid 27.1.41 and the product is hydrolyzed by an alkali (base that dissolves

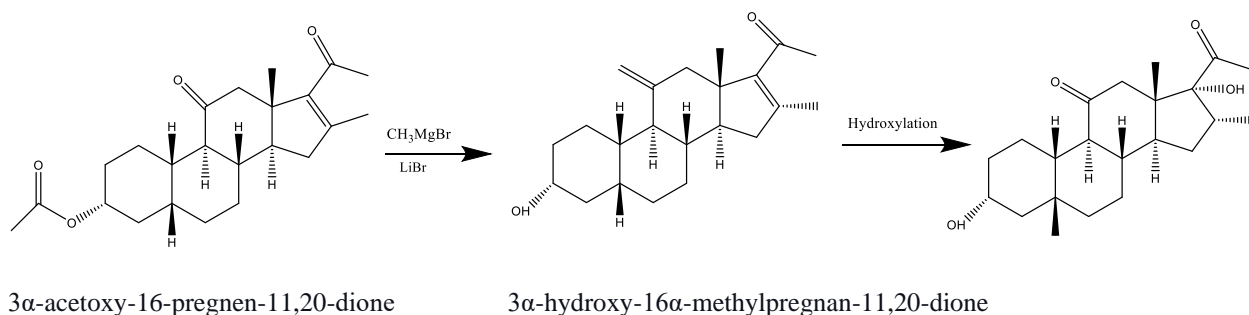
²¹ Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veessler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*

²² Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., ... & Du, B. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive care medicine*, 12

²³ Parikh, K., Hall, M., Mittal, V., Montalbano, A., Gold, J., Mahant, S., & Shah, S. S. (2015). Comparative effectiveness of dexamethasone versus prednisone in children hospitalized with asthma. *The Journal of Pediatrics*, 167(3), 639

²⁴ Vardanyan, R., & Hruby, V. (2006). *Synthesis of essential drugs*. Elsevier

in water) to produce oxyketone 27.1.42. Further, C21, as a hydroxyl group, is added to the product through subsequent bromination of molecular bromine, a methyl group. The bromine atom is replaced with iodine. Iodine is reacted with potassium acetate to form acetoxyketone 27.1.43.²⁵ The C3, which is the hydroxyl group, is further oxidized to a carbonyl by Chromium (Vi) oxide in pyridine forming 3,11,20-triketone 27.1.44.²⁶ The product further undergoes brominating with *Semicarbazide* forming an unsaturated triketone 27.1.45. The final product is treated with pyruvic acid to prevent semicarbazone formation at the keto-groups at C3 and C20. 21-*O*-acetoxy-16 β -methylhydrocortisone (27.1.46) is formed upon the removal of protective semi-carbzone groups. Additionally, epoxide 27.1.49 is formed upon reacting to the product with potassium acetate. Hydrofluoric acid is reacted with the product to form fluorohydrin 27.1.50.²⁷ The compound is dehydrogenated at C1-C2 and simultaneous dehydrogenation to produce dexamethasone



Scheme 1. Synthesis of Corticosteroids

Therefore, through the preparation, the study seeks to understand why the manufacturing process is suitable to treat the current virus after a long search of the covid-19 vaccine. As of June 2020, scientists reported that dexamethasone would cut the risk of death by a third of patients on

²⁵ Vardanyan, R., & Hruby, V. (2006). *Synthesis of essential drugs*. Elsevier

²⁶ Ibid.

²⁷ Ibid.

ventilators, while individuals on oxygen would be cut by a fifth. Hence, through an investigation in dexamethasone's manufacturing process, it would answer how it is suitable for Covid-19 treatment.

Dexamethasone is part of the steroid drugs. For medical conditions with inflammations may cause the immune systems to be overworked. The overworking of the body may result in organ or tissue damage. Steroids like dexamethasone assist in blocking the immune system to respond to inflammation, thus preventing the damage.²⁸ For adrenal insufficiency, the use of dexamethasone assists in replacing the hormones that are produced by the adrenal gland.²⁹ The adrenal assist the body assists in controlling various body functions like metabolisms, response to stress, and blood pressure. Dexamethasone can interact with various medications, herbs, and vitamins. An interaction denotes an instance when a substance changes ways of working on a drug. Avoiding interaction would call for the doctor to manage the situation carefully. According to Alhazzani et al. (2020), dexamethasone has an effect on innate and adaptive immunity. The adaptive immunity is integral to the covid-19 immunopathology, which is the imine response connected to the disease. Even if the dexamethasone is recommended to treat Covid-19, it is unclear whether the corticosteroids are the vest treatment for every patient with Covid-19.

2.0 The Biological Activity of Dexamethasone

Secondly, the clinical uses of Dexamethasone and side effects will be analyzed in the study. However, researchers like Vardy et al. (2006)³⁰ already proposes some of the dexamethasone uses like treatment of allergic reactions, certain skin, and eye conditions, immunes/blood/hormone

²⁸ Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., ... & Du, B. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive care medicine*, 1-34.

²⁹ Fernandes, N. (2020). Economic effects of coronavirus outbreak (COVID-19) on the world economy. *Available at SSRN 3557504*

³⁰ Vardy, J., Chiew, K. S., Galica, J., Pond, G. R., & Tannock, I. F. (2006). Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. *British journal of cancer*, 94(7), 1011

disorder systems, breathing problems, certain cancers, and certain bowel disorder. Additionally, Jia et al.³¹ present side effects of dexamethasone: increased appetite, irritability, insomnia, heartburns, and increased blood sugar levels.

Fourth, the study will focus on covid-19 as part of coronavirus that has left the world devastated with huge losses of life and businesses. Humans' social nature makes it hard to contain covid-19 as an infectious disease that continues to impact the world. As part of the viral diseases that continuously mutate, the success of securing a single vaccine for Covid-19 has proved difficult. Thus, the study will establish why dexamethasone is suitable for treating Covid-19. Under this subheading, the study will focus on its definition, structure, diagnosis, symptoms, and the impacts of Covid-19 on research and development of possible vaccines.

Next, the study examines dexamethasone as a treatment of Covid-19. Scientists capitalize on the ability of dexamethasone to dampen down the body's immune system. In most cases, the coronavirus infection leads to inflammation as the human body tries to fight it off.³² However, the immune system may go overdrive, and the reaction may prove fatal. Thus, dexamethasone is designed to calm the effects of such a reaction between the antibodies and the viruses. Under this section, the structure of dexamethasone unique for treatment of Covid-19 will be exposed towards appreciating a breakthrough in the fight against covid-19.

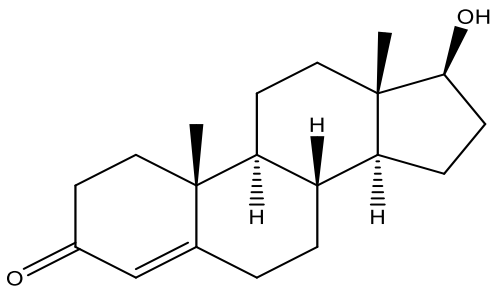
Lastly, the study focuses on the conclusion and future work of dexamethasone, as well as the fight to find a vaccine for covid-19. Under its research and development team, the WHO is committed to making significant progress on the covid-19 vaccine search. Additionally, this

³¹ Jia, M., Deng, C., Luo, J., Zhang, P., Sun, X., Zhang, Z., & Gong, T. (2018). A novel dexamethasone-loaded liposome alleviates rheumatoid arthritis in rats. *International journal of pharmaceuticals*, 540, 1

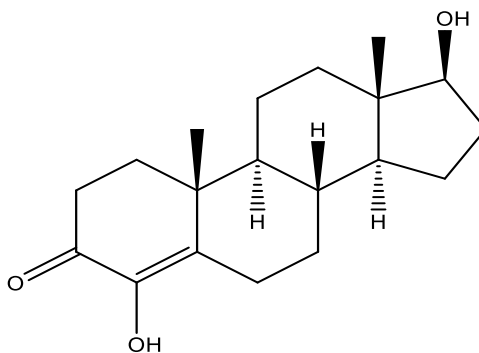
³² Meng, L., Hua, F., & Bian, Z. (2020). Coronavirus disease 2019 (COVID-19): emerging and future challenges for dental and oral medicine. *Journal of Dental Research*, 99(5), 481

article's future adds to the existing studies towards understanding the behavior of the viruses towards developing vaccines.

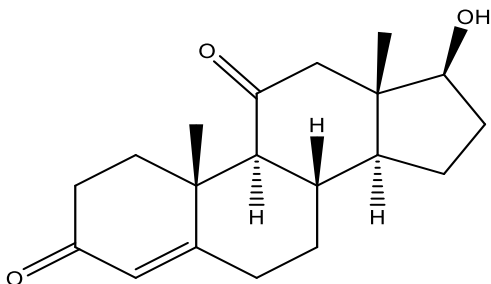
Chemical structures of some steroid hormones:



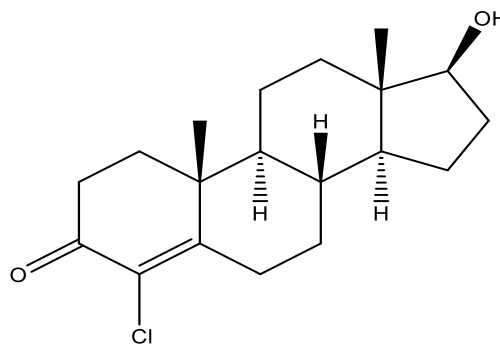
Testosterone



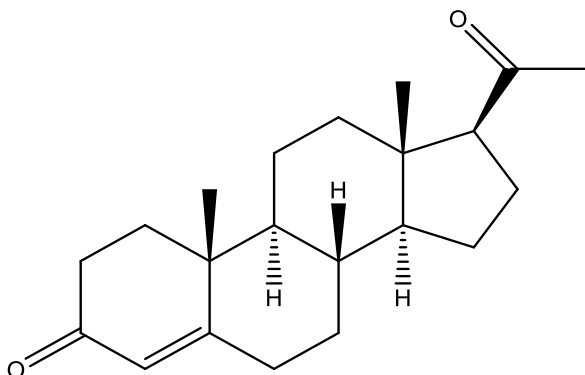
4-Hydroxytestosterone



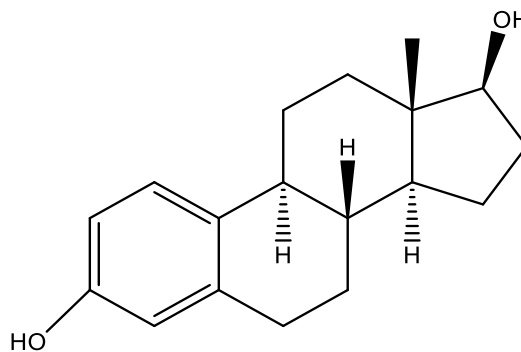
11-Ketotestosterone



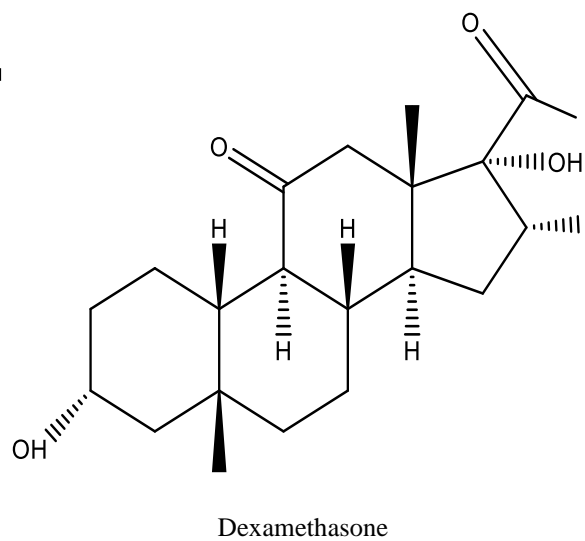
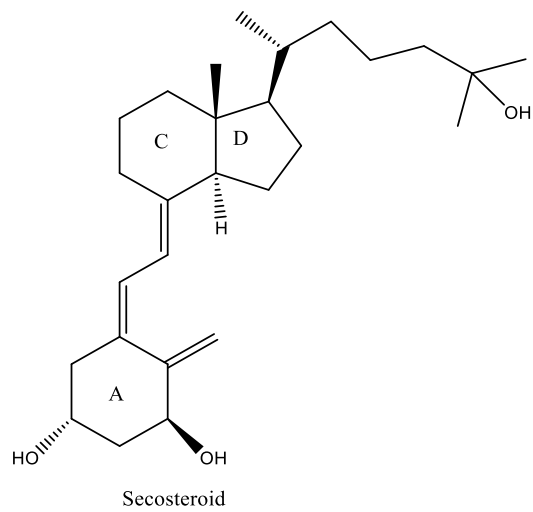
4-Chlorotestosterone



Progesterone



Estradiol



Reference

- Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., ... & Du, B. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive care medicine*, 1-34. doi.org/10.1056/NEJMoa2002032
- Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology*, 17(3), 181-192. DOI: [10.1038/s41579-018-0118-9](https://doi.org/10.1038/s41579-018-0118-9)
- De Nicola, A. F., & Deniselle, M. C. G. (2019). Introduction to the Special Issue “Neuroactive Steroids”. doi.org/10.1007/s10571-019-00657-9
- Duffy, S. (2018). Why are RNA virus mutation rates so damn high? *PLoS biology*, 16(8), e3000003. doi.org/10.1371/journal.pbio.3000003
- Eurosurveillance Editorial Team. (2020). Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. *Eurosurveillance*, 25(5), 200131e. doi.org/10.2807/1560-7917.ES.2020.25.5.200131e
- Fernandes, N. (2020). Economic effects of coronavirus outbreak (COVID-19) on the world economy. Available at SSRN 3557504. <http://dx.doi.org/10.2139/ssrn.3557504>
- Jia, M., Deng, C., Luo, J., Zhang, P., Sun, X., Zhang, Z., & Gong, T. (2018). A novel dexamethasone-loaded liposome alleviates rheumatoid arthritis in rats. *International journal of pharmaceutics*, 540(1-2), 57-64. doi.org/10.1016/j.ijpharm.2018.02.001
- Kuba, K., Imai, Y., Rao, S. *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 11, 875–879 (2005). <https://doi.org/10.1038/nm1267>

- Ling Ni, Fang Ye, Meng-Li Cheng, Yu Feng, Yong-Qiang Deng, Hui Zhao, Peng Wei, Jiwan Ge, Mengting Gou, Xiaoli Li, Lin Sun, Tianshu Cao, Pengzhi Wang, Chao Zhou, Rongrong Zhang, Peng Liang, Han Guo, Xinquan Wang, Cheng-Feng Qin, Fang Chen, Chen Dong. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. *Immunity*, 2020; DOI: [10.1016/j.immuni.2020.04.023](https://doi.org/10.1016/j.immuni.2020.04.023)
- Meng, L., Hua, F., & Bian, Z. (2020). Coronavirus disease 2019 (COVID-19): emerging and future challenges for dental and oral medicine. *Journal of Dental Research*, 99(5), 481-487. doi.org/10.1177/0022034520914246
- Parikh, K., Hall, M., Mittal, V., Montalbano, A., Gold, J., Mahant, S., & Shah, S. S. (2015). Comparative effectiveness of dexamethasone versus prednisone in children hospitalized with asthma. *The Journal of Pediatrics*, 167(3), 639-644. doi.org/10.1016/j.jpeds.2015.06.038
- Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., ... & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*. doi.org/10.1016/j.ijssu.2020.02.034
- Spiga, O., Bernini, A., Ciutti, A., Chiellini, S., Menciasci, N., Finetti, F., ... & Niccolai, N. (2003). Molecular modelling of S1 and S2 subunits of SARS coronavirus spike glycoprotein. *Biochemical and biophysical research communications*, 310(1), 78-83. doi.org/10.1016/j.bbrc.2003.08.122
- Vardanyan, R., & Hruby, V. (2006). *Synthesis of essential drugs*. Elsevier.
- Vardy, J., Chiew, K. S., Galica, J., Pond, G. R., & Tannock, I. F. (2006). Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. *British journal of cancer*, 94(7), 1011-1015. doi.org/10.1038/sj.bjc.6603048

Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veerler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*. doi.org/10.1016/j.cell.2020.02.058