كلية الصيدلة

DRUG INFORMATION CENTER BULLETIN
FACULTY OF PHARMACY
ASSIUT UNIVERSITY

Ass. Uni. D.I. Bull., Vol. 16, No. 2, June 2020

F-750-30-07

جامعة أسيوط

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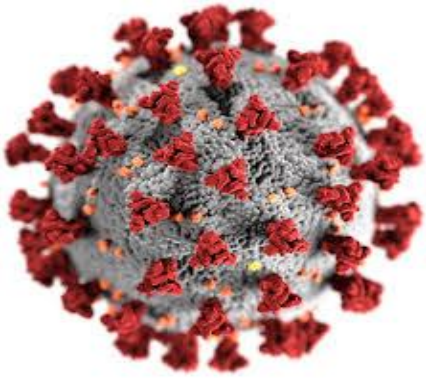
رقم الايداع: 12632 لسنة 2005

This Bulletin is a free quarterly periodical issued by theDrug Information Center (DIC) located at Faculty of Pharmacy Assiut University

COVID-19

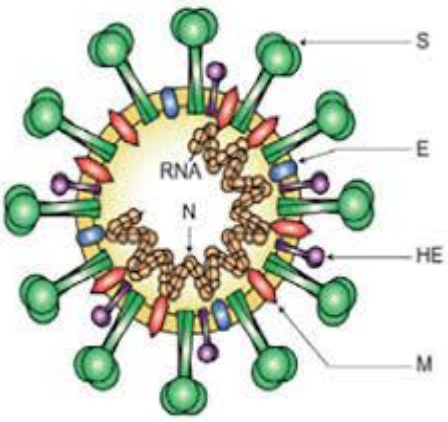
History of SARS-CoV-2 (COVID-19)

An acute respiratory syndrome (ARDS) episode was identified in Wuhan, China; and officiallydesignated as COVID-19 (previously known as "novel coronavirus 2019") by the WHO.WHO declared COVID-19 outbreak a global pandemic on 11th March 2020. It is caused by SARS-CoV-2 that is likely associated with zoonotictransmission. COVID-19 has influenced 186 nations.The clinical and genetic characteristics of SARSCoV-2 support the similar pathogenesis pattern between SARS-CoV and MERS-CoV. The elevated level ofcytokine release during the infection caused the failure of multiple organs leading to the patient death. Treatment of patients depends on the clinical course and symptoms associated with the COVID-19. Several prevention and control measures including; active surveillance, use of masks, and hand sanitizers are recommended to manage the spread of the infection.COVID-19 was sampled using a throat swab to detect the viral nucleic acid usingReal Time Polymerase Chain Reaction (RT-PCR), for early detection and treatments evaluation. Here, we comprehensively summarized the corona virus structure,mechanism of action, epidemiology, pathogenesis, and management and prevention of COVID-19



CoronavirusStructure of COVID-19

SARSCoV-2 is a β Coronavirus of sub-genus Botulinum belongs to coronaviridae group, and is the third known zoonotic coronavirus. as the coronavirus genome is comprised of ~30000 nucleotides. It encodes four structural proteins, Nucleocapsid (N) protein, Membrane (M) protein, Spike (S) protein and Envelop (E) protein and several non-structural proteins (nsp) .The capsid is the protein shell, inside the capsid, there is nuclear capsid or N-protein which is bound to the virus single positive strand RNA that allows the virus to hijack human cells and turn them into virus factories. The N protein coats the viral RNA genome which plays a vital role in its replication and transcription. The N-terminal of the N protein which is binding to genomic and sub-genomic RNAs in MHV and IBV virions and process the viral replication and transcription.



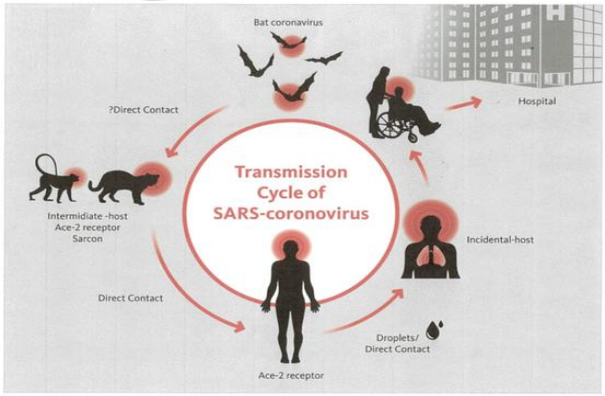
Two important class of compounds, theophylline and pyrimidone drugs,have been reportedas possible inhibitors of RNA binding to the N terminal domain of N protein of coronavirus, thus opening new avenues for in vitro validations.

The M-protein is most abundant in the viral surface and it is believed to be the central organizer for the coronavirus assembly. The S-protein is integrated over the surface of the virus, it mediates attachment of

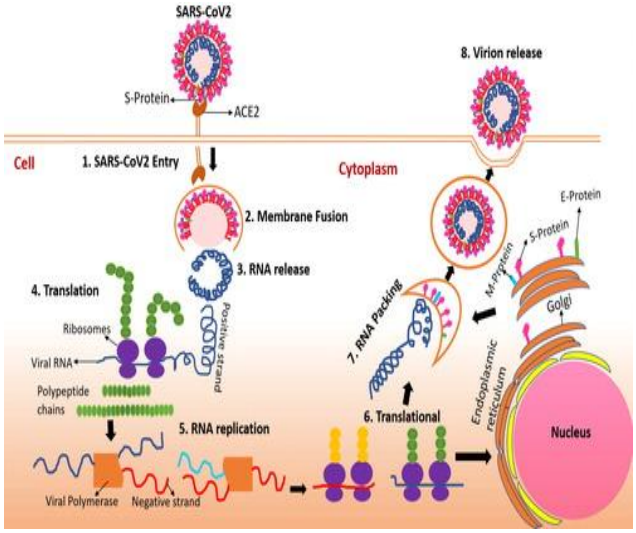
the virus to the host cell surface receptors and fusion between the viral and host cell membranes to facilitate viral entry into the host cell.The E-protein is a small membrane protein composed -76 to 109 amino-acid and minor component of the virus particle, it plays an important role in virus assembly, membrane permeability of the host cell and virushost cell interaction.A lipid envelop encapsulates the genetic material. Hemagglutinin-esterase dimer (HE) have been located on the surface of the viral. The HE protein may be involved in virus entry, is not required for replication, but appears to be important for infection of the natural host-cell .State-of-the-art cryo-EM experiments have revealed the full structure of the Spike (S) protein in the close and open (prefusion) states . Such glycoprotein is made of three identical chains with 1273 amino acid each and it is composed by two well-defined protein domain regions: S1 and S2 subunits which are associated to cell recognition and the fusion of viral and cellular membranes respectively. The latter processoccurs through different protein conformational changes that remain still uncharacterized.

Trasmission of COVID-19

Based on the large number of infected people that were exposed tothe wet animal market in Wuhan City where live animals are routinely sold, it is suggested that this is the likely zoonotic origin of the COVID-19.However, to date, there has been no consistentevidence of coronavirus reservoirs other than mammals and birds Genomic sequence analysis of COVID-19 showed 88%identity with two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses indicating that mammals are the most likely link between COVID-19 and humans. Several reports have suggested that person-to-person transmission is a likely route for spreading COVID-19 infection. Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual.The binding of a receptor expressed by host cells is the first step of viral infection followed by fusion with the cell membrane. In a small study conducted on women in their third trimester who were confirmed to be infected with the coronavirus, there was no evidence that there is transmission from mother to child.



Mechanism of action of COVID-19



The coronavirus spike (S) proteinattaches to angiotensin converting enzyme 2 (ACE2) receptors that is found on the surfaceofhumancells, including those in the lungs allowing virus entry. The coronavirus S proteinissubjectedtoproteolyticcleavages by host proteases (i.e. trypsin and furin), in two sites located at the boundary between the S1 and S2 subunits (S1/S2 site). In a later stage happens the cleavage of the S2 domain (S20 site) in order to release the fusion peptide.This event will trigger the activation of the membrane fusion mechanism. Searching for antibodies can find support on molecular targeting which can utilize the structural information(as sequence) of the binding region which is found in angiotensin-converting enzyme 2 receptor. In this way this protocol could device a treatment to block the viral entry.Typically, human cell ingests the virus in a process called endocytosis. Once entered the cytoplasm, it has been suggested most likely that COVID-19 employs a unique threestep method for membrane fusion, involving receptor-binding and induced conformational changes in Spike (S) glycoprotein followed by cathepsin L proteolysis through intracellular proteases and further activation of membrane fusion mechanism within endosomes .Then, the endosome opens to release virus to the cytoplasm, and uncoating of viral nucleocapsid (N) is started via proteasomeswhich typically can hydrolyse endogenous proteins, but they are also capable of degrading exogenous proteins.A different two-step mechanism has been suggested: in this case the virion binds to a receptor on thetarget host cell surface through its S1 subunit and the Spike is cleaved by host proteases and then itis expected the fusion at low pH between viral and host target membranes via S2 subunit. Finally, the viral genetic material a single stranded RNA is fully released into the cytoplasm. There takes place the replication and transcription processes which are mediated by the so-called replication/transcription complex (RTC). Such complex is encoded in theviral genome and it is made of non-structural proteins(nsp).The RTC is believed to induced double-membrane structuresin the cytoplasm of the infected cell .Following the positive RNA genome is translated togenerate replicase proteins from open reading frame 1a/b(ORF 1a/b).

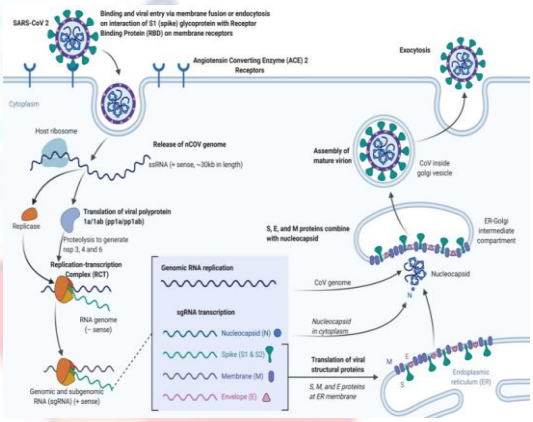
These proteins use the genome as a template to generated full-length negative sense RNAs,which subsequently serve as templates in generatingaddition full-length genomes. Structural viral proteins, M, Sand E are synthesized in the cytoplasm and then insertedinto the endoplasmic reticulum (ER) and transfer to endoplasmic reticulum-Golgi intermediate compartment (ERGIC).Also, in the cytoplasm nucleocapsids are formed from the encapsidation of replicated genomes by N protein, and as a result they coalesce within the ERGIC membrane in order to self-assembly into new virions. Finally, novel virions are exported from infected cells by transport to the cell membrane in smoothwalled vesicles and then secreted via a process called exocytosis,so that can infect other cells. In the meantime, the stress of viral production on the endoplasmic reticulum eventually leads to cell death. However, the mechanism of action for novel COVID-19 is still unknown.

Epidemiology of COVID-19

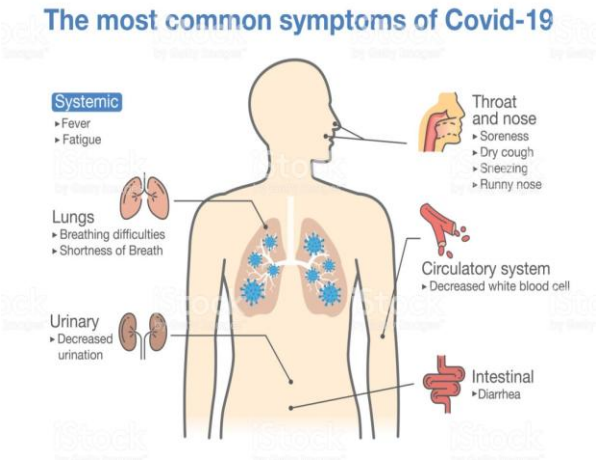
As of 19th June 2020, over 8.45 million cases have been diagnosed globally with more than 453,000 fatalities. In the 14 days to 19 June, more than 1.85 million cases were reported.Egypt ranked 70 in the death rate by precent of (3.86%), the recovery rate (26.7),in 19thJune 2020 the total number of infected patients is around 52211 cases.It has been reported that the most affected age groups are above +80 years old: 14.8% death rate, followed by70-79 years: 8%, 60-69 years: 3.9%, 50-59 years: 1.3%, and finally the 40-49 years: 0.4% death rate. The least affected ages are 10-39 years recording 0.2% death rate. Males have a higherdeath rate of 4.7%, followed by females with 2.8% deaths of confirmed cases. The associated comorbiditiesare cardiovascular diseases: 13.2% death rate, diabetes: 9.2%, chronic respiratory diseases: 8%,hypertension: 8.4%, cancer: 7.6% and 0.9% deaths were associated with no any underlying diseases.

Pathogenesis of COVID-19

It has been demonstrated that the virus might proceed via the mucous membranes,particularly the nasal and throat mucosa, then ingress into the lungs via the respiratory tract. The alveolar epithelial cells in the lungs are found to be thefundamental cell affected by the SARS-CoV-2 virus.The S protein has been revealed as a remarkable impetus of the virus entry into host cells. The envelope spike glycoprotein ties up to its biological receptor ACE2, adjacent to alveolar epithelial cells in the lungs. After that, the SARS-CoV-2 spikes bind ACE2 with around 10 folds higher affinity than SARS-CoV. Thispromotes the transmission properties of SARS CoV2.



Moreover, CD209L and CD209 arebelieved to be elective receptors through which the virus attaches the cells; however the mechanism is poorly understood.The recent studies revealed that following entry of the virus into the cells,the viral RNA genome is liberated into the cytoplasmand is expressed into two poly proteins and structuralproteins, after which the viral genome begins toreplicate. The recently established envelopeglycoproteins are lodged into the sheet of theEndoplasmic reticulum or Golgi gadget, and then thenucleocapsid is re-organized by the union of genomicRNA and nucleocapsid protein. Then, viral fragmentssprout into the Endoplasmic reticulum-Golgiintervening section. Finally, the vesicles containing thevirus fragments meld with the plasma membrane toliberate the virus by exocytosis.The virus may enter



the peripheral blood from thelungs, provoking viremia. At that time, the virus willbombard the additional targeting organs that expressACE2, such as the heart, kidney, and thegastrointestinal tract. while the viral fragment enters the cell, the antigen isacquainted with the antigen-presenting cell by theMHC/HLA system. These are seen through the unequivocal cytotoxic T-cells response. This antigen can make the sporadic T-cell response in light ofprompting of the T-cell apoptosis. The latest reports released also showed the enormous decline of the $CD4^+$ and $CD8^+$T cells in the peripheral blood of the COVID-19 patients.Numerous assessments reported by the uncontrolled central combustible responses against the virus by the provocative cytokines (cytokinestorm) such as; IFN α, INF-γ, IL - 1β, IL-6, IL-12, IL-18, IL-3, TNF-α, TGF-β, IL-2, IL-10, MCP1, IL-1RA,etc., and by the raised degrees of chemokines including; CCL2, CCL3, CXCL8, CXCL9, CXCL10,etc. The cytokine storm triggered by the immune system generates obstructions in the respiratory system leading to Acute Respiratory Distress Syndrome(ARDS) and finally causing death. However, more immune-associated investigations are required to assist us in interpreting the pathogenesis of the disease.

Management of COVID-19

There are many different drug therapies trials on coronavirus-positive patients worldwide in an effort to find a potential COVID-19 treatment.Here, we will highlight the proposed treatments as follows:-

1. **Remdesivir**

   Remdesivir is an antiviral that is given by intravenous (IV) infusion in the hospital. This is a brand-new drug that has not been approved by the FDA for use on the market yet, and is being tested in carefully controlled environments. It was previously shown to have some effect against SARS, MERS, and Ebola in cell and animal models. In a recent in vitro study Remdesivir prevented human cells from being infected with SARS-CoV-2 (the virus that causes COVID-19).Early results from a large study of 1,063 patients showed that hospitalized patients who got Remdesivir recovered faster than those who got a placebo (11 days vs. 15 days, respectively). The death rate in the Remdesivir group (7%) was also lower than that of the placebo group (12%). Patients who needed oxygen saw the most benefit with Remdesivir. the researchers concluded that treatment with Remdesivir alone is likely not enough as still experienced a high death rate.

2. **Dexamethasone**

   Dexamethasone is a common corticosteroid (steroid) medication that has been used for many years to treat various health conditions, such as autoimmune conditions and allergic reactions. RECOVERY, a randomized clinical trial in the UK, is studying many medications, including dexamethasone, to see if any are effective against COVID-19. A press release reported that there was a lower death rate in the 2,104 hospitalized patients with COVID-19 who got a low, daily dose of dexamethasone (either by mouth or IV injection) compared to the 4,321 patients who did not get it. The medication seemed to be most helpful for patients who were on a ventilator (35% lower death rate) or needed extra oxygen (20% lower death rate); there was no benefit for those with less severe symptoms, it's difficult to draw any strong conclusions.

3. **Hydroxychloroquine and chloroquine**

Hydroxychloroquine and chloroquine are two medications that have been used for many decades to treat malaria and autoimmune conditions like rheumatoid arthritis and lupus. A few small studies suggest that they may also be helpful for treating hospitalized patients with mild cases of COVID-19, while many other studies showed that hydroxychloroquine did not make a difference.

4. **Azithromycin**

Azithromycin is an antibiotic commonly used to treat bacterial infections such as bronchitis and pneumonia. It has been shown to have some in vitro activity against viruses like influenza A and Zika, but did not work against the coronavirus that causes MERS. One research group looked at azithromycin in combination with hydroxychloroquine for COVID-19. They reported that 93% of patients cleared the virus after 8 days, but there was no control group so we don't know if people would have cleared the virus on their own without the medications. There are concerns about potentially serious side effects when using azithromycin and hydroxychloroquine together.

5. **Convalescent plasma**

On March 24, 2020, the FDA issued an Emergency Investigational New Drug (eIND) application for the use of convalescent plasma to treat people with COVID-19. Plasma is the liquid part of blood that carries blood cells. Convalescent plasma is collected from people who have recovered from COVID-19. It is then transfused into someone with an active coronavirus infection. It is thought that antibodies found in the convalescent plasma can help fight the coronavirus infection.In China, 10 adults with severe COVID-19 symptoms were given convalescent plasma. The researchers reported that all symptoms (such as fever, cough, shortness of breath, and chest pain) had greatly improved within 3 days. Compared to a historic control group (a random group of patients who were previously hospitalized for COVID-19), the group who received convalescent plasma saw better improvements in their health.

6. **Actemra (tocilizumab)**

Actemra is a disease-modifying anti-rheumatic drug (DMARD) approved for rheumatoid arthritis and juvenile idiopathic arthritis. (Both are inflammatory diseases.) It works by blocking interleukin-6 (IL-6), a protein involved in our natural immune responses. IL-6 normally signals other cells to activate the immune system, but too much activation can cause issues. One possible serious issue with an overactive immune system is a cytokine storm, a potentially fatal problem in which the immune system goes haywire and inflammation gets out of control. With COVID-19, people can be at risk of cytokine storms as their bodies continue to ramp up their immune system to fight off the infection. By blocking IL-6, Actemra helps to calm down the immune system and is believed to also help with managing cytokine storms. A study from France reported that people who got Actemra were less likely to require ventilation or die.

7. **Kaletra (lopinavir/ritonavir)**

Kaletra is an HIV medication containing a combination of two antivirals called lopinavir and ritonavir. In vitro and clinical studies looking at patients who had previously received these antiviral agents suggest that they may have some activity against SARS and MERS (infections caused by other coronaviruses). Data for using Kaletra in COVID-19 is limited.In one randomized study of 199

people hospitalized with COVID-19, there was no difference between using Kaletra and not using it in terms of how long it took for patients to improve. Another study of 127 people with mild COVID-19 symptoms looked at Kaleta alone compared to Kaletra in combination with interferon beta-1b and ribavirin. They found that the group who got all three medications improved sooner and cleared the virus faster (7 days) than those who only got Kaletra (12).

8. **Tamiflu (oseltamivir)**

   Tamiflu is an antiviral medication used for influenza (flu). Results from a hospital in Wuhan, China were not promising. Of 138 hospitalized patients, 124 got Tamiflu along with other medications. By the end of the study, 85 patients (62%) were still hospitalized and 6 had died. Nonetheless, several clinical trials are currently looking at Tamiflu in combination with other medications for coronavirus.

9. **Avigan (favipiravir) and other antiviral medications**

   Favipiravir (also known as Avigan) is an antiviral medication approved in Japan and China for the flu. In vitro studies have shown that high doses of favipiravir were able to prevent human cells from being infected with SARS-CoV-2.Two studies in China looked at how favipiravir worked in comparison to other antivirals. In a study of 240 patients in China with mild COVID-19 symptoms, 71% of patients given favipiravir recovered after 7 days compared to 56% who were given umifenovir (Arbidol). Another small study in China looked at 80 patients with mild COVID-19 symptoms and saw that that favipiravir helped to clear the virus faster than Kaletra (4 days vs. 11 days, respectively). The patients who took favipiravir also showed greater improvements in their lungs based on chest images.

10. **Other antivirals**

    Other antivirals being tested for COVID-19 include umifenovir and galidesivir. Galidesivir is a new drug that is currently being developed for a variety of viral infections; it has not yet been approved for human use. Clinical trials for galidesivir are starting in Brazil.

11. **Colcrys (colchicine)**

    Colchicine is a medication used for gout. It works in many different ways, including activating anti-inflammatory processes and interfering with cells involved in inflammation. Researchers think that colchicine could work similarly to Actemra in COVID-19 patients in that it might be helpful if the immune system becomes too activated and a cytokine storm occurs. A large clinical trial is currently seeing if colchicine, when given soon after a COVID-19 diagnosis, can lower the chances of hospitalization and death.

12. **Ivermectin**

    Ivermectin is an oral medication used to treat infections caused by parasites. It is also available as a lotion or cream to treat lice and rosacea. A recent in vitro study found that ivermectin can stop SARS-CoV-2 from replicating. A lot more research is needed to see if the doses studied would be safe and effective against the virus in humans.

FDA-approved treatments for coronavirus (COVID-19)

There are currently no FDA-approved treatments for coronavirus. The FDA recently created a new emergency program, Coronavirus Treatment Acceleration Program (CTAP), aimed at speeding up research for the development of COVID-19 treatments.For now, the treatment for patients with mild symptoms is to self-isolate at home. Patients who are hospitalized receive supportive care (such as oxygen), enroll in clinical trials, and are given medications off-label based on hospital guidelines and their doctors' clinical judgement.

Is there a cure or vaccine for COVID-19?

There is no cure or vaccine for COVID-19 at this time. More studies are needed to confirm if any of the potential treatments listed above will work for COVID-19.

Gereral Advices:

1- **Healthy diet**

Eating a diet of fresh healthy foods in reasonable amounts is the best way to get your daily dose of vitamins and minerals.

2- **Antioxidant-rich foods**

A diet rich in antioxidants has been linked to a host of health-promoting, disease-fighting activities in the body".These vitamins and mineals include:

a) Vitamin A and beta-carotene: pumpkin, squash, carrots, spinach, sweet potatoes, cantaloupes, dark leafy greens, and mangoes
b) Vitamin C: citrus fruits, strawberries, bell peppers, cauliflower, broccoli, tomatoes, sweet potatoes, and asparagus
c) Vitamin D: Fatty fish, like tuna, mackerel, and salmon, orange juice, soy milk, cereals,Beef liver, Cheese and Egg yolks.
d) Vitamin E: vegetable oil, almonds, whole grains, wheat germ, sweet potatoes, and yam
e) Selenium: salmon and haddock
f) Zincsupplements: meat , eggs, cheese, nuts ,rice ,wheat ,dark choclate and beans .

Some evidence shows vitamins C, D, E, and zinc supplements are beneficial for respiratory infections with symptoms similar to COVID-19, although no major studies have been published on their effects on the novel coronavirus.Zinc in sufficient amounts has shown some evidence of reducing the length of some viral infections when taken right away. Studies have shown this using zinc lozenges, syrups, and tablets.The body needs zinc to create white blood cells that fight infections.

3- Exercise

Along with a healthy diet and adequate nutrition, there are other healthy activities like excerzie that can re-enforce your immune health. Moderate exercise has been shown to improve the flu-fighting power of vaccines in seniors. During the COVID-19 outbreak, staying home and being away outdoor exercise partners, it has encouraged solo exercises include jogging, jumping rope and yoga.

4- Stress Reduction

Stress can be reduced through breathing exercises, meditation, working out, talking to a therapist, and getting out into nature, along with many other ways.

5- Sleep

Getting the right amount of quality sleep can help your natural infection resistance. Sveral studies have suggested a link between sleep and a healthy immune system.

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