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SECOSTEROID VITAMER AS MICRONUTRIENT TO DEFEAT AIRBORNE CORONAVIRUS

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ABSTRACT:

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and multiple other biological effects. In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol). Interest in a potential role for vitamin D in the prevention or treatment of acute respiratory infections dates back to the 1930s, when cod liver oil was investigated as a means to reduce industrial absenteeism due to the common cold. Meta-analyses of randomised controlled trials conducted from 2007–20 reveal protective effects of vitamin D against acute respiratory infections, albeit these effects were of modest size and with substantial heterogeneity. The striking overlap between risk factors for severe COVID-19 and vitamin D deficiency, including obesity, older age, and Black or Asian ethnic origin, has led some researchers to hypothesise that vitamin D supplementation could hold promise as a preventive or therapeutic agent for COVID-19. From a mechanistic angle, there are good reasons to postulate that vitamin D favourably modulates host responses to severe acute respiratory syndrome coronavirus. (SARS-CoV-2), both in the early viraemic and later hyperinflammatory phases of COVID-19. Vitamin D metabolites have long been known to support innate antiviral effector mechanisms, including induction of antimicrobial peptides and autophagy. Laboratory data relating to effects of vitamin D on host responses to SARS-CoV-2 specifically are scarce, but one study that screened four compound libraries for antiviral activity has reported an inhibitory effect of the active vitamin D metabolite 1,25-dihydroxyvitamin D (the steroid hormone and biologically active vitamin D metabolite) in human nasal epithelial cells infected with SARS-CoV-2. Vitamin D has also been shown to regulate immunopathological inflammatory responses in the context of other respiratory infections. The finding that these effects were mediated via regulation of the renin-angiotensin system (RAS) in an animal model has particular relevance in the context of severe COVID-19, where overactivation of RAS associates with poor prognosis. Epidemiological studies investigating links between circulating levels of 25-hydroxyvitamin D (25[OH]D; the biomarker of vitamin D status) and incidence and severity of COVID-19 are currently limited in number. Two ecological studies have reported inverse correlations between national estimates of vitamin D status and COVID-19 incidence and mortality in European countries. Lower circulating 25(OH)D concentrations have also been reported to associate with susceptibility to SARS-CoV-2 infection and COVID-19 severity. Recently, it has shown that airway diseases are associated with dysregulated vitamin D metabolism, raising the possibility that vitamin D deficiency might arise as a consequence of pulmonary inflammation. Prospective studies can provide insights into the potential for reverse causality, but results from those published to date are conflicting: one retrospective longitudinal study from Israel reported independent associations between low pre-pandemic 25(OH)D levels and subsequent incidence and severity of COVID-19, but an analogous study in the UK showed no such associations. Both of these studies are potentially limited by the use of historic 25(OH)D measurements, which might not reflect concentrations at the time of exposure to SARSCoV-2. They are also open to residual and unmeasured confounding. Mendelian randomisation studies offer one approach to overcome these problems, but they need to be very large to detect small or moderate effects which might still be of clinical significance. In the view, well powered randomised controlled trials of vitamin D supplementation for the prevention and treatment of COVID-19 are now needed to test for causality. A number of hospital-based treatment trials have been registered to date, but it may prove challenging to detect a signal for vitamin D supplementation in severe COVID-19 for two reasons. First, patients tend to present to hospital in the hyperinflammatory stage of the disease, so it might be too late for them to benefit from any antiviral effects induced by vitamin D supplementation. Second, it could be hard to show the effect of a micronutrient over and above dexamethasone, which has potent anti-inflammatory actions and now represents the standard of care in severe disease. Prevention of SARS-CoV-2 infection also represents an ambitious target, given the highly infectious nature of the pathogen. Perhaps the best hope for showing a clinical benefit lies in a population-based trial investigating prophylactic vitamin D supplementation as a means of attenuating the severity of incident COVID-19, to the extent that it is either asymptomatic or does not result in hospitalisation. The design of such a trial should be informed by findings of meta-analyses of randomised controlled trials of vitamin D to prevent other acute respiratory infections, which suggest that the intervention would work best when given in daily doses of 400–1000 IU to individuals with lower baseline vitamin D status. Pending results of such trials, it would seem uncontroversial to enthusiastically promote efforts to achieve reference nutrient intakes of vitamin D, which range from 400 IU/day in the UK to 600–800 IU/day in the USA. These are predicated on benefits of vitamin D for bone and muscle health, but there is a chance that their implementation might also reduce the impact of COVID-19 in populations where vitamin D deficiency is prevalent; there is nothing to lose from their implementation, and potentially much to gain.

KEYWORDS:

VITAMERS, SECOSTEROIDS, CHOLECALCIFEROL, CALCIFEDIOL, ERGOCALCIFEROL, HYDROXYERGOCALCIFEROL.

INTRODUCTION:

Several forms (vitamers) of vitamin D exist. The two major forms are vitamin D2 or ergocalciferol, and vitamin D3 or cholecalciferol; vitamin D without a subscript refers to either D2 or D3 or both. These are known collectively as calciferol. Vitamin D2 was chemically characterized in

1931. In 1935, the chemical structure of vitamin D3 was established and proven to result from the ultraviolet irradiation of 7-dehydrocholesterol.[1,2]

Chemically, the various forms of vitamin D are secosteroids, i.e., steroids in which one of the bonds in the steroid rings is broken. The structural difference between vitamin D_2 and vitamin D_3 is the side chain of D_2 that contains a double bond between carbons 22 and 23, and a methyl group on carbon 24. A secosteroid (/ˈsɛkoʊˌstɛrɔɪd/) is a type of steroid with a "broken" ring. The word secosteroid derives from the Latin verb secare meaning "to cut",:241 and 'steroid'. Secosteroids are alternatively described as a subclass of steroids or derived from steroids. Types or subclasses of secosteroids are defined by the carbon atoms of the parent steroid skeleton where the ring cleavage has taken place. For example, 9,10-secosteroids derived from cleavage of the bond between carbon atoms C9 and C10 of the steroid B-ring (similarly 5,6-secosteroids, 13,14-steroids, etc.). The prototypical secosteroid is cholecalciferol (vitamin D3). Some nonsteroidal estrogens, like doisynolic acid and allenolic acid, are also secosteroids or secosteroid-like compounds.[3]

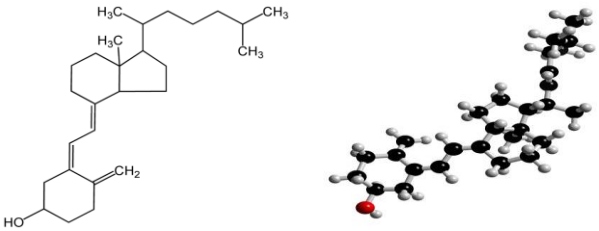
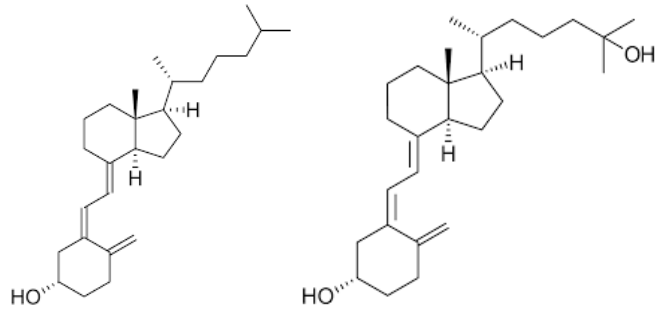


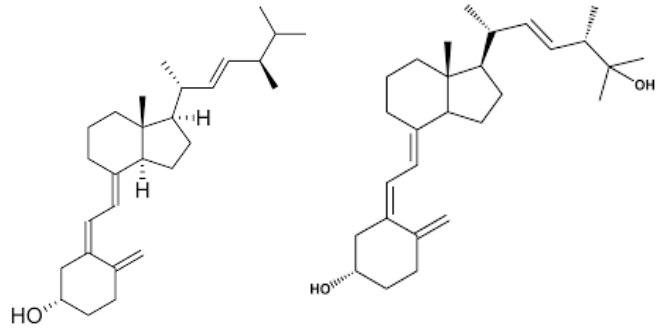
FIGURE-1: CHEMICAL & 3D STRUCTURE OF VITAMIN D

Natural & Synthetic Sources Of Vitamin-D: The major natural source of the vitamin is synthesis of cholecalciferol in the lower layers of skin epidermis through a chemical reaction that is dependent on sun exposure (specifically UVB radiation). Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements. Only a few foods, such as the flesh of fatty fish, naturally contain significant amounts of vitamin D. In the U.S. and other countries, cow's milk and plant-derived milk substitutes are fortified with vitamin D, as are many breakfast cereals. Mushrooms exposed to ultraviolet light contribute useful amounts of vitamin D. Dietary recommendations typically assume that all of a person's vitamin D is taken by mouth, as sun exposure in the population is variable and recommendations about the amount of sun exposure that is safe are uncertain in view of the skin cancer risk.

Vitamin D from the diet, or from skin synthesis, is biologically inactive. It is activated by two protein enzyme hydroxylation steps, the first in the liver and the second in the kidneys. As vitamin D can be synthesized in adequate amounts by most mammals if exposed to sufficient sunlight, it is not essential, so technically not a vitamin. Instead it can be considered a hormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol, which then produces effects via a nuclear receptor in multiple locations.[4]



Cholecalciferol **Calcifediol**



Ergocalciferol **Hydroxyergocalciferol**

FIGURE-2: SECOSTEROIDS

Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites (called 25-hydroxyvitamin D or 25(OH)D) are measured in serum to determine a person's vitamin D status. Calcifediol is further hydroxylated by the kidneys to form calcitriol (also known as 1,25-dihydroxycholecalciferol), the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, having a major role regulating the concentration of calcium and phosphate, and promoting the healthy growth and remodeling of bone. Calcitriol also has other effects, including some on cell growth, neuromuscular and immune functions, and reduction of inflammation.[5]

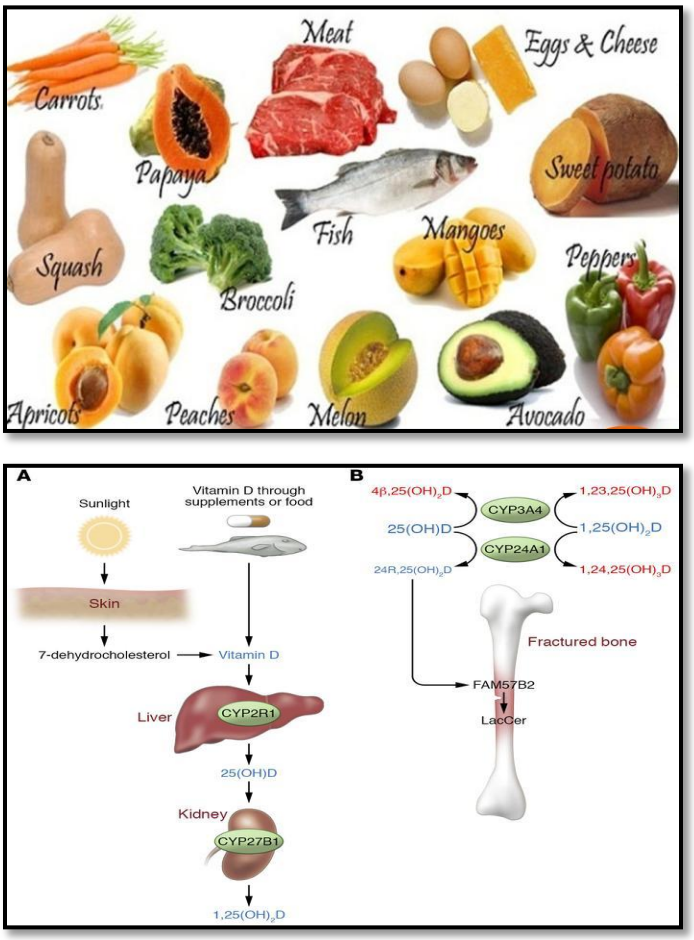


FIGURE-3: VITAMIN D NATURAL & SYNTHETIC SOURCES

BIOLOGY: The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine. The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast.

VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content.

One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body. Thus, vitamin D is also critical for bone remodeling through its role as a potent stimulator of bone resorption.

The VDR regulates cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells. In vitro, vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells, and affects the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione.[6]

Vitamin D receptor expression decreases with age and findings suggest that vitamin D is directly related to muscle strength, mass and function, all being important factors to an athlete's performance.

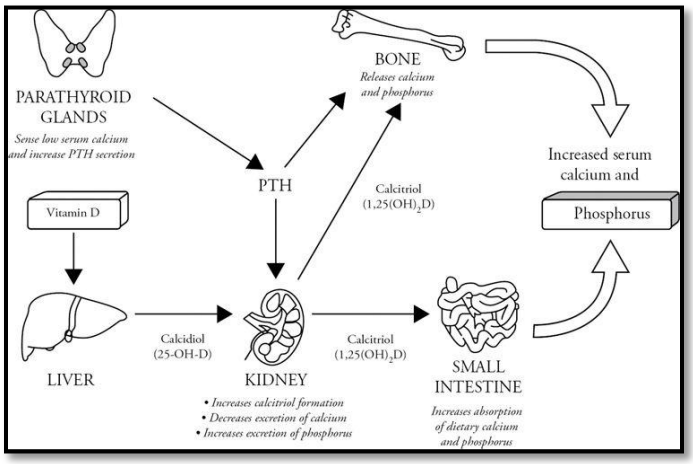


FIGURE-4: CALCIUM METABOLISM

IMPORTANCE OF VITAMIN-D IN COVID-19 PANDEMIC SITUATION: The COVID-19 pandemic raised concerns that vitamin D deficiency may be a risk factor for respiratory infection, but there is only preliminary evidence of a direct association between vitamin D deficiency and COVID-19 infection. One UK study found no association between previously measured vitamin D levels and the incidence of COVID-19 infection when adjustments were made for potential confounding factors, such as ethnicity. Vitamin D deficiency is prevalent in many countries with the highest numbers of COVID-19 cases and deaths, such as the United States, Spain, the UK, Italy, and Iran. An evidence summary published by the UK NICE concluded there was nothing to support the use of vitamin D supplements for the prevention or treatment of COVID-19.

According to ClinicalTrials.gov, several Phase II-IV clinical trials are underway to assess the use of vitamin D for prevention or treatment of COVID-19 infection, with most in preliminary stages and none completed, as of May 2020. Most trials have the design of studying COVID-19-infected people who are vitamin D deficient.[7]

FIGURE-5: VITAMIN D, A NEW RAY OF HOPE TO STOP COVID-19 PANDEMIC

The evolving list of what makes someone "high risk" for severe COVID-19—darker skin, older age, and obesity, for example—aligns closely with risk factors of vitamin D deficiency, research shows. As a result, some scientists are proposing that vitamin D deficiency may be directly connected to increased risk of severe COVID-19.

Tiffany Joy Yamut

Covid-19 immunoregulation

FIGURE-6: BUILD IMMUNITY SAY NO TO COVID-19

"Vitamin D plays an important role in our immune systems," Tiffany Joy Yamut, RN, a registered nurse and co-founder of diet resource site Ketogenic Buddies, tells Verywell. "This may explain why being deficient in vitamin D, which is common in Europeans due to low UV exposure, can increase a person's likelihood of being infected and hospitalized." Because vitamin D is known to help prevent respiratory infections, several different studies have explored the potential role it could play in COVID-19.[8]

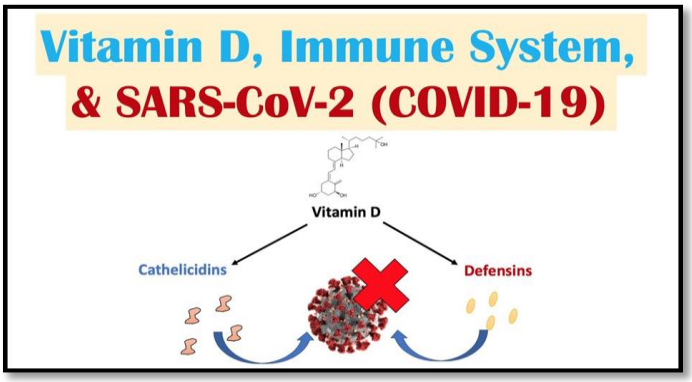


FIGURE-7: MODE OF ACTION OF VITAMIN D IN COVID-19

VITAMIN D DEFICIENCY & COVID-19 RISK: In a May study published in *Aging Clinical and Experimental Research*, researchers from the U.K. looked at data from 20 different European countries, comparing the rates of COVID-19, as well as the death tolls from the disease, with the population's vitamin D levels. They reported that countries experiencing higher death rates, like Italy and Spain, also have higher rates of vitamin D deficiency or inadequacy. On the other hand, countries with lower rates of vitamin D deficiency, like Denmark, Sweden, and Norway, have lower rates of COVID-19 infection and mortality.

The researchers also pointed out that vitamin D levels are "severely low" in the aging population, especially in Spain and Italy. In a smaller study, which was pre-printed in July but has yet to be peer-reviewed, researchers compared prevalence of COVID-19 cases to vitamin D levels in the general population *prior* to the start of the pandemic. This study, which was pre-printed in July but has yet to be peer-reviewed, analyzed data from 10 countries, including the US, China, Germany, Italy, and Iran. Researchers found a strong correlation between the rates of vitamin D deficiency and severe complications and/or death from COVID-19. In another pre-printed study, researchers from the University of Chicago Medicine looked at the charts of 499 patients who had their vitamin D levels measured within one year of being tested for COVID-19. They found that patients who had a clinical vitamin D deficiency that was not corrected were almost twice as likely to become infected with COVID-19 than patients who had normal vitamin D levels.

VITAMIN D & IMMUNE SYSTEM: Both severe infections and deaths in COVID-19 patients are often linked to an overreaction of the immune system, called a "cytokine storm," that's triggered by the virus. When the immune system overreacts, it produces an excessive amount of pro-inflammatory cytokines that can trigger acute respiratory distress syndrome, or ARDS, and widespread tissue damage that can cause organ failure and death.

Targeting cytokines, and trying to prevent or stop this cytokine storm, could be the answer to reducing severity of COVID-19 infections and increasing survival rates, researchers say. Vitamin D could help. According to a January 2020 report in *Nutrients*, vitamin D decreases the expression of pro-inflammatory cytokines while simultaneously increasing the expression of anti-inflammatory cytokines. In other words, vitamin D helps reduce the compounds that cause inflammation while producing more of the compounds that decrease inflammation—a combination that could prevent a cytokine storm. Yamut explains that vitamin D also stimulates the production of cathelicidin, an antimicrobial peptide that helps fight off viruses, bacteria, and fungi. She adds that this could at least partially explain why vitamin D deficiency can lead to viral infections and hospitalization.[9]

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SKEPTICISM ABOUT VITAMIN D & COVID-19: Even though vitamin D is intricately connected to the immune system, some health professionals aren't convinced that it's the answer to protecting against COVID-19. The results from the above studies drew criticism from a group of doctors from Yale. These doctors say that correlation doesn't equal causation and, even though vitamin D is vital to immune health, it's too soon to say whether or not the vitamin is significant when it comes to severity of COVID-19 infection. Another concern is that the general population will interpret the results incorrectly. Kathleen Suozzi, MD, a Yale Medicine dermatologic surgeon, expressed concern that media coverage of the studies will cause people to take excessive amounts of vitamin D supplements, or even sunbathe too much. While vitamin D toxicity is rare, taking too many supplements can lead to side effects like nausea, vomiting, poor constipation, and weakness. It can also raise the level of calcium in your blood, leading to complications like muscle cramps, irregular heart beat, and even kidney failure.

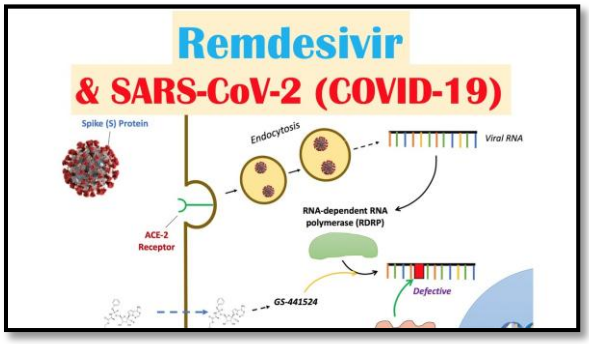
A review of the studies by the National Institute for Health and Care Excellence (NICE) in the U.K. pointed out that because they are not intervention studies, which measure the effectiveness of a treatment or prevention method, we still don't have any information on how much vitamin D is protective, or whether or not there are adverse effects of taking vitamin D with an active COVID-19 infection.[10]

HOW MUCH VITAMIN D YOU NEED: Even though vitamin D may not be the panacea for COVID-19, it's still an important part of a healthy diet. In addition to keeping your immune system healthy, vitamin D also plays roles in:

- Calcium balance
- Thyroid health and hormone balance
- Heart health
- Insulin secretion
- Optimal muscle function and bone health

Exactly how much vitamin D you need depends on your health and current vitamin D levels, but the general guidelines from the National Institutes of Health are:

- **Babies and infants (up to 12 months):** 400 IU (international units)
- **Children and adults ages 1 to 70:** 600 IU
- **Adults over 70 years:** 800 IU



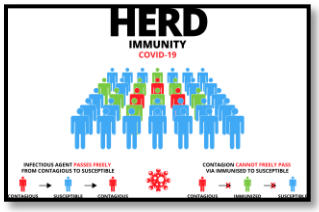
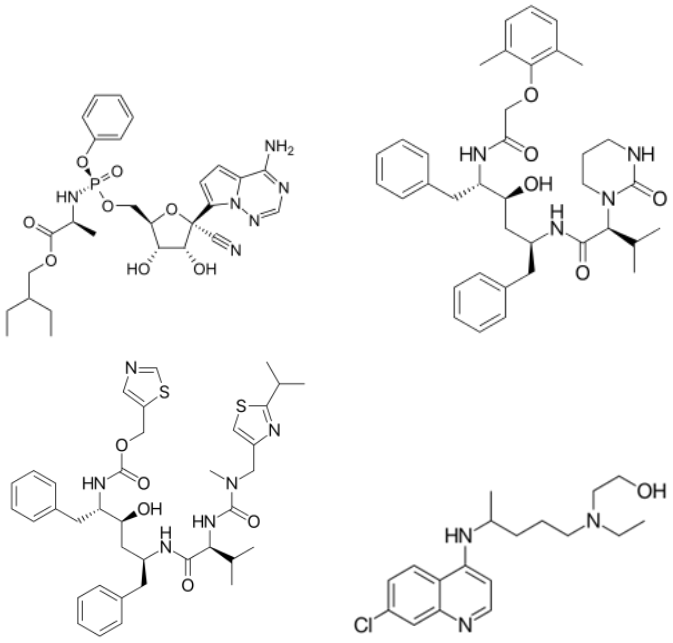


FIGURE-8: IMMUNOSUSCEPTABLE TO CONTAGIOUS VICE VERSA



REMDESIVIR

[(2*S*)-2-{(2*R*,3*S*,4*R*,5*R*)-[5-(4-Aminopyrrolo[2,1-*f*] [1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]phenoxy-(*S*)-phosphorylamino}propionic acid 2-ethyl-butyl ester]

LOPINAVIR

[(2*S*)-*N*-[(2*S*,4*S*,5*S*)-5-[2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide**]**

RITONAVIR [1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-methyl-2-{[methyl({[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl})carbamoyl]amino}butanamido]-1,6-diphenylhexan-2-yl]carbamate]

HYDROXYCHLOROQUINE
[(RS)-2-[{4-[(7-chloroquinolin-4-yl)amino]pentyl}(ethyl)amino]ethanol]

These are the main drugs are used for Covid-19 but no drug is approved for coronavirus by FDA. All are used as a human trial for Covid-19 as guided by WHO. Alternative treatment of any flu type of infection is a causative by virus. Coronavirus is made up of RNA strands which is airborne pathogen directly hits in the alveoli of lungs having spikes nature to be embedded in the mucosal layer of pulmonary region to be accumulated into the liquid tissue like plasma and lymph. Infected people may be hydrated sufficiently with taking fluid diet like fruit juice for few days with proper sunlight for photons to produce activation of ergosterol into cholecalciferol and air not in isolated in airconditioned room which prevents the immune system to be charged into embracement the total body system to become natural activation. We have to increase the body immunity to fight against the virus. Lockdown or social distance or thermal gunning or isolation or masking is not the solution to protect the coronavirus form living system. Not only covid millions of virus are in our environment but we are living with the virus from the beginning of the earth and many viruses are accustomed with our immune system of immunoglobulins and those immunoglobulins which are weak in nature are being defeated by the viral attacks. So, to increase the immunity & herd immunity is the solution to empower the power of stamina. So, we need well balanced food with sufficient macronutrients [carbohydrates, proteins, lipids] and micronutrients [Vit-A, Vit-C, Vit-D, minerals] and fresh air [O_2], sunlight [photons=hυ] with sufficient physical activities. Many people are not attached with nature and their immunity automatically reduces and chance of infection increases.

CONCLUSION: As the Covid-19 pandemic continues to spread, the need to understand which populations are most at risk of developing severe disease or dying from Covid-19 grows ever more critical. Recent studies have found an association between vitamin D and Covid-19 severity and mortality. Vitamin D may protect from viral infection and ameliorate the symptoms of Covid-19, including the cytokine storm.

One of the recent vitamin D studies demonstrated that in 20 European countries, an association exists between low levels of vitamin D and higher numbers of Covid-19 cases and mortality. Vitamin D levels are found to be severely low for the older population in these countries, especially in Spain, Italy, and Switzerland. As these are some of the more vulnerable populations to developing Covid-19, this might play an important role in vulnerability to the disease.

Another recent Indonesian retrospective cohort study of 780 Covid-19 patients indicated that the majority of death cases had below-normal vitamin D levels and that vitamin D status was strongly associated with Covid-19 mortality.

Vitamin D has a known effect on the immune system, as previous studies have found an association between susceptibility to respiratory tract infections and low vitamin D levels. Vitamin D levels being low have been associated with numerous factors including older age, less sun in the winter, darker skin pigmentation, exposure to less sunlight, and diet. Diets rich in vitamin D, such as those that include fatty fish, orange juice, cheese, and eggs yolks, can help prevent vitamin D deficiency, along with supplementing vitamin D.

Higher vitamin D levels are found in northern Europe due to a diet heavy in cod liver oil and a higher amount of vitamin D supplements. Scandinavian nations have lower numbers of Covid-19 cases compared to the rest of Europe. Italy is one of the worst affected European countries, and has very high levels of vitamin D deficiency, especially in the elderly. Increased pigmentation results in reduced vitamin D production via sun exposure. Individuals in institutions, such as hospitals and care homes, are more likely to be severely deficient in vitamin D due to lack of sun exposure or diet.

Vitamin D plays a role in the functioning of the immune system and modulates white blood cells by preventing them from releasing too many inflammatory cytokines. This could help lessen the Covid-19-induced cytokine storm. Vitamin D also helps to reduce lung injury and reduces the risk of acute respiratory tract infections.

Because about 40% of the US population is vitamin D deficient, understanding the role vitamin D plays in Covid-19 immune response could help reduce the mortality of the disease.

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