



COVID-19 PATHOLOGY AND VITAMIN D NANOEMULSION AS PREVENTIVE AND ALTERNATIVE REMEDIATION FOR SEVERITY: A REVIEW

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ABSTRACT

Today, CoVID-19 has infected 3,635,483 worldwide and has claimed the lives of 251,577 people and it continues to affect more lives. To date, no drug has been completely tested for the disease and prospective vaccines are still being studied. Meanwhile, various parts of the world have shown positive results using Vitamin D as a possible cure and preventive measure for viral infection including CoVID-19 because of its immune modulation participation in both the innate and adaptive immunity both of which influence pathogen invasion. Clinical studies have shown that the overwhelming host immune response to the CoVID-19 that may be responsible for the severity and mortality could be regulated with Vitamin D which has been shown to modulate inflammatory responses during viral infection. Nanoemulsions of vitamin D could be potentially more effective as preventive and alternative remediation for CoVID-19 severity.

KEYWORDS: CoVID-19, Coronavirus, vitamin D, nanoemulsion.

INTRODUCTION

The CoVID19 pandemic has turned the world's healthcare providers rummaging for ways to halt the spread of the disease which as of today, May 16 has infected 4,616,726 people worldwide and has taken 307,955 lives.^[1] The world as we know it has changed into a mostly bare place with people indoors, even though, still a few are daring to be outdoors in spite of the threat of coming down fast with this disease. Having been in quarantine or lockdown and observing social distancing since March 15, people have made their best efforts to cope with the changes. The healthcare system, the healthcare providers and the scientists have tried their best and continue to try their best to find a fast cure or vaccine that will put an end to this threat. Various existing drugs with known curative effects for some other diseases have been tapped like the hydroxychloroquine, a drug for arthritis that is also prescribed for malaria.^[2] But efforts in France have shown that there has been no evidence of clinical efficacy of hydroxychloroquine in hospitalized patients that are suffering from CoVID-19 infection with oxygen needs.^[3] Remdesivir, the drug that was used to treat SARS and MERS coronaviruses was prescribed to one patient in Washington state who survived.^[4] The use of Remdesivir in the USA, Canada or Europe and in Japan had 47% discharged and 36% death.^[5] With this global

pandemic from the Coronavirus, the possible curative effect of vitamins based on their possible effects on the immune system that had long been studied and established using viral infections provide hope.

SARS-CoV-2 causes CoVID-19

The Coronavirus disease of 2019 (CoVID-19) is the disease that is caused by the new virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) which is genetically similar to the SARS Coronavirus of 2002 (SARS-CoV-1).^[6] The SARS-CoV-2 is a 50-200 nm diameter enveloped single stranded RNA (ribonucleic acid)^[7] that is 30 Kb. Among the genome encoded structural proteins is the spike glycoprotein (S) which is a viral fusion protein located on the surface of the outer envelope.^[8] The coronavirus S glycoprotein is a precursor protein that gets cleaved into three S1/S2 heterodimers that assemble into a trimer spike on the surface of the virus. This step is a critical part in viral infection which the virus uses to identify the host cell receptors that is followed by subsequent fusion of the viral and cellular membranes.^[9] The trimer spike has been shown to bind to angiotensin-converting enzyme 2 (ACE2) membrane exopeptidase that converts Angiotensin I to the nonapeptide angiotensin. ACE2 is expressed in human airway epithelial pneumocytes which are the cells lining the air sacs in the lung, lung

parenchyma and in epithelial lining of the oral cavity that possibly causes easy access for the SARS-CoV-2 infection.^[10,11] Additionally, ACE2 expression has also been found in lymphocytes in the oral mucosa and in organs of the digestive system. After SARS-CoV-2 enters the pneumocyte cells through endocytosis it multiplies in the cytoplasm imposing a high rate of production of viral proteins on the pneumocytes causing apoptosis. Meanwhile, after the entry of the RNA from the SARS-CoV-2, it releases its genetic contents and the host cells activate the pattern recognition receptors (PRRs) which is the innate immune response which is the first line of defense that detect the viral infection. The three major classes of PRRs include Toll-like receptors (TLRs), retinoic acid inducible gene 1-like receptors (RLRs) and NOD-like receptors (NLRs).^[12] The TLRs which are associated with the membrane recognize the pathogen-associated molecular patterns (PAMP) and also viral coat proteins^[13] which induce the production of interferons (IFN).^[14] Another set of PRRs located in the cytoplasm are the RLRs and NLRs that respectively sense viral dsRNAs or bacterial cell wall components.^[15] When the virus has fused the S glycoprotein with the membrane, it releases its genome RNA into the cytoplasm of the host cell which translates polyproteins to create replication-transcription complex^[16] which in turn synthesizes sub-genomic RNAs^[17] that contain the codes for structural and accessory viral proteins.^[18] In the presence of endoplasmic reticulum and Golgi bodies of the host, the sub-genomic RNAs and the new viral proteins assemble to form viral particle buds which fuse with the plasma membrane to release the virus.^[19] The SARS CoV-2 has been found to exhibit genomic similarity to SARS CoV-1 in the S-glycoprotein gene and the receptor binding domain which suggests the capability for direct human transmission.^[18] Important findings at the protein level are the mutations in some non-structural proteins that play a role in the infectious capability and differentiation of the SARS CoV-2^[20] which are important to understand the host infectivity and transmission between SARS CoV-1 and the SARS CoV-2.^[18] Studies that focused on the analysis of the genotype of CoVID-19 in different patients from several provinces in China found that SARS CoV-2 had been mutated.^[21] In a population genetic analyses conducted on 103 SARS CoV-2 genomes showed two prominent evolution types, the L (70%) and the S (30%) types^[22] where the strain from L that were derived from S type were more aggressive.

Upon entry of the SARS-CoV-2 into the host, immune response is vital for the control and elimination of the infections before it causes immunopathogenesis that is associated with out of control immune response^[18]. On contact, the S proteins of SARS-CoV-2 binds to the ACE2 with a 10 times higher affinity than SARS-Cov-1 to the host cells and has a higher threshold for virus infection.^[23] After attachment to the host, membrane fusion follows and release of the viral RNA which are detected by PRRs results in a cascade of reactions that

activate the innate immune system leading to the formation of type I Interferons (IFN- α / β) and a series of pro-inflammatory cytokines.^[24,25,26] A properly regulated innate immune response could eliminate the virus or else immunopathology would come in. In CoVID-19 patients, plasma cytokines and chemokines including IL-1, IL-2, IL4, IL-7, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (MCSF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), interferon gamma induced protein 10 (IP-10), granulocyte colony-stimulating factor (GCSF), IFN- γ and tumor necrosis factor- α (TNF- α), hepatocyte growth factor (HGF).^[27,28,29] have been prevalent. Studies on patients indicated that the virus particles initially invaded the respiratory mucosa then infected other cells which resulted in a series of immune responses that led to over production of cytokines which may have resulted in the life-threatening condition of COVID-19 patients.^[18] Low levels of nutrients^[30,31] such as vitamins A, B, C and D^[32] as well as Se, Zn and Fe are important to assess in CoVID19 patients^[33,34] because low levels during viral infections have been associated with adverse conditions.^[35,36]

The Immune System

The human immune system consists of three levels of defense which are the 1) primary barriers that maybe physical of chemical, 2) innate immunity, and 3) adaptive immunity. The primary barriers include both the physical (i.e. intact skin, mucosal clearance mechanisms) and chemical barriers (low pH in the stomach and lysozymes in tears, saliva and other fluid secretions).^[37,38] The innate immunity is the first immunological defense that hosts have against the attacks from foreign invaders such as infectious bacteria, virus and other agents. Innate immunity refers to the initial reaction of the host cell to defend itself from the threats of a foreign invaders. Thus, because this is naturally present and not caused by past events, it is not exclusive to a specific pathogen or virus or event and depends on a group of phagocyte cells which immediately attack, devour and get rid of the foreign invaders that enter the body. These phagocyte cells include the macrophages which are found in tissue and the neutrophil granulocytes which are found in the blood and tissue. The innate immune system is supported by enzymes which are called upon to mark the invaders, attract other immune cells from the blood, dissolve the cell walls of the invaders, or destroy virus envelope. Marked invaders become susceptible to the natural killer cells which attack and dissolve them using cytotoxins. When the innate immune response is unsuccessful in 4-7 days, it calls on the adaptive immune response into active duty.

The adaptive immune response is specific in its action and it remembers the invaders by producing memory cells. The adaptive immune response belongs to white blood cells called lymphocytes which are either antibody

responses or the cell-mediated immune responses. The adaptive immune response produces B lymphocytes, T lymphocytes, antibodies, and cytokines both in the blood and tissue. The B lymphocytes produce antibodies in the blood which are specific for exactly one pathogen and are sent out to bind and destroy the pathogen. The T lymphocytes have characteristics that bind to the specific pathogen and in the process develop into T helper cells, T killer cells or cytotoxic T cells, memory T cells or regulatory T cells. The T cells could express Toll-like receptors, CD4, CD8, and CD25 receptors which play a role in recognition and activation. The combined activities of the adaptive immune response interact by binding directly to the cells or use and produce messenger cells such as the cytokines to destroy invading pathogens and eliminate any toxic molecules they produce.

CoVID-19 Pathology and Immune response

In China, during the initial stages of the Covid-19 outbreak, diagnosis of the disease was convoluted by the variety of symptoms, imaging results and gravity of disease.^[39] Upon patient presentation, fever was identified in 43.8% but was developed in 88.7% after hospitalization and severe conditions occurred after admission in 15.7%. In a separate report on the kinetics of immune response from a mild CoVID-19 case that was hospitalized, blood analysis indicated increased antibody-secreting cells (ASCs), follicular helper T cells (TFH cells), activated CD4+ T cells and CD8+ T cells and immunoglobulin M (IgM) and IgG antibodies that bound the coronavirus SARS-CoV-2 before symptomatic recovery.^[40] These immunological changes persisted for at least 7 days following full resolution of symptoms. From day 7 to day 20, progressive increase in SARS-CoV-2-binding IgM and IgG in plasma were detected. The co-expression of CD38 and HLA-DR on CD8+ T cells rapidly increased in this woman from day 7 (3.57%) to day 8 (5.32%) and day 9 (11.8%), then decreased at day 20 (7.05%). These observation about CD38+HLA-DR+ T cells were similarly documented in a 50-year-old man with CoVID-19.^[41] Relative to healthy individuals, co-expression of CD38 and HLA-DR on CD4+ T cells increased between day 7 (0.55%) and day 9 (3.33%) in the woman, relative to that of healthy donors (0.63% ± 0.28%; n = 5). Preceding the resolution of the symptoms, rapid increase in activated CD38+HLA-DR+ T cells, especially CD8+ T cells, at days 7–9 was recorded. Immunopathology indicated CD16+CD14+ monocytes, showed lower frequencies of CD16+CD14+ monocytes in the blood at days 7, 8 and 9 than in healthy control, possibly indicative of the efflux of CD16+CD14+ monocytes from the blood to the site of infection. This patient exhibited recruitment of immune cell populations (ASCs, TFH cells and activated CD4+ and CD8+ T cells), together with IgM and IgG SARS-CoV-2-binding antibodies, in the patient's blood before the resolution of symptoms.

Vitamin D as preventive and alternative remedy for CoVID-19 virulence

Although the virulence mechanism of the coronavirus causing CoVID-19 has not been fully understood, some virulence mechanisms have been identified.^[42,43] It has been reported that in CoVID-19 infection, the human DPP-4/CD26 interact with S1 domain of the virus spike glycoprotein.^[44] Corrective levels of vitamin D exhibited reduction in the DPP4/CD26 receptor expression levels^[45] plus other clinical outcomes during infection^[46,47] including CoVID-19 infection. Downregulation of proinflammatory cytokines^[48] has been exhibited in the presence of vitamin D. In human cell lines and other studies vitamin D was activated in lung tissue with a consequent preventive effect on respiratory viral infection.^[49,44,50] A paper by Hansdottir and Monick^[51] indicated a direct correlation between low vitamin D levels and vulnerability to infections in the lungs. These may all be related to the immune system modulator effect of vitamin D which prevents the overexpression of inflammatory cytokines while enhancing the oxidative potential of macrophages. Vitamin D could enhance the production of anti-microbial peptides found in neutrophils monocytes, natural killer cells and the epithelial cell lining of the respiratory tract.^[52] As of yet, the research results are insufficient but there are reports that indicate the pathways that are linked to the vitamin D receptors. These include HLA-DR, CD8, CD4 and CD38 which is a glycoprotein that is expressed in immune cells which perform significant roles in innate and adaptive immune function.

Very recently, a letter published by Dr. Alipio from the Philippines reported the outcomes of a study that was carried out on 212 cases with confirmed CoVID-19^[53] patients. In his letter, he addressed the observation that serum levels of 25OHD was lowest in severe cases and was highest in patients with mild symptoms. A pre-print paper by Meltzer et al indicated the correlation between vitamin D deficiency and the risk of CoVID-19.^[54] In forty one (41) CoVID-19 patients, the initial plasma levels of IL1, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFN γ , IP10, MCP1, MIP1A, MIP1B, PDGF, TNF α , and VEGF concentrations were higher in patients regardless of whether they were in ICU patients or not compared with healthy controls.^[55] Between ICU and non-ICU patients, plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF α were higher in ICU patients than non-ICU patients and all had pneumonia. The patients also had high levels of IL1B, IFN γ , IP10, and MCP1, which could have led to activated T-helper-1 (Th1) cell responses^[52]. The patients needing ICU admission had higher levels of GCSF, IP10, MCP1, MIP1A, and TNF α which indicated cytokine storm associated with disease severity compared with those that were non-ICU admissions. The patients initiated increased secretion of T-helper-2 (Th2) cytokines (eg, IL4 and IL10) that suppress inflammation.

As exhibited in the clinical studies of CoVID-19 patients, the overwhelming host immune response to the viral infection causing immunopathology leads to the severity and mortality risks to viral diseases.^[56,57] Studies have shown that vitamin D modulates the cytokine response in animal models of autoimmune diseases by controlling the production of proinflammatory cytokines like the tumor necrosis factor α and interleukin-12 (IL-12) causing the suppression of inflammation.^[58] Mechanism of the inflammatory response modulation with vitamin D to regulate the levels of cytokines, inhibit NF- κ B signaling pathway, and inhibition of the immune cells (macrophages, DCs, B cells, and T cells) has been well documented.^[59] Vitamin D has been reported to enhance *IL-10* gene expression and inhibit the *Th1*- and *Th2*-specific transcription factors.^[60] Another study indicated the down-regulation of *IL-8* in hyperinflammatory macrophages with high doses of 25OHD, 1,25OHD and the synthetic analogue paricalcitol.^[61] IL-6 which is another pro-inflammatory cytokine is regulated by 25OHD^[62] while the immunoglobulin production from B cells of lupus patients are decreased with 1,25OHD.^[63]

Vitamin D has been shown to inhibit B cell proliferation, block B cell differentiation, and immunoglobulin secretion.^[64,65] It suppresses T cell proliferation^[66], causes shift from Th1 to Th2 phenotype.^[67] and facilitates the induction of T regulatory cells.^[68] Such activities control the production of inflammatory cytokines (IL-17 and IL-21) while increasing anti-inflammatory cytokines (IL-10) (Aranow paper). Vitamin D also inhibits the monocyte production of the inflammatory cytokines IL-1, IL-6, IL-8, IL-12 and TNF α .^[69] Piemonti et al reported that vitamin D inhibits differentiation and maturation of monocyte derived DCs and that macrophages secrete 1,25OHD in immune microenvironments.^[70]

In many infectious and autoimmune diseases, vitamin D is recognized to mitigate the extent of immunity as well as help regenerate the endothelial lining that could minimize lung damage. Studies have shown that in either bacterial or viral acute respiratory tract infection, vitamin D supplementation brings a 12% overall protective effect.^[71] The VDR in immune cells increase in the presence of infection. In the presence of calcitriol, the stimulation of CD4⁺ CD25⁻ T cells prevent the production of pro-inflammatory cytokines, including IFN- γ , IL-17, and IL-21 without disturbing T cell division.^[72] T-cell cytokines IFN- γ , a Th1 cytokine, up-regulates bioconversion of 25(OH)D₃ to its active metabolite, calcitriol, while the Th2 cytokine IL-4 induces conversion to the inactive metabolite 24,25OHD.^[73] The succession of these immune events which are stimulated by vitamin D suppress the formation of pro-inflammatory cytokines, including IFN- γ , IL-17, and IL-22, except IL-4 in CD4⁺ T cells.^[74] In a separate study, it was suggested that vitamin D limits autoimmunity by diverting CD4 T cells from producing

IL-9 in favor of IL-10^[75] and suppresses inflammatory infiltrates and the expression of IL-17.^[76] It has been reported that actions of Vit D family were mediated by the vitamin D receptor (VDR).^[77] Knowing all these effects of vitamin D on the immune response to infection, it has been taunted as a potential cure as well as a preventive remedy for CoVID-19.^[78] There are several ways to take vitamin D as preventive as well as a possible alternative cure for CoVID-19.

The devastating effect of the CoVID-19 pandemic compels taking urgent action to prevent overwhelming the healthcare system and the health of the communities especially because the onset of the disease may be asymptomatic during the first few days. This immediate action may involve targeting enhancement of the human immune system. Mounting evidences suggest that vitamin D is an immune modulator during respiratory infections.^[79,80,81] As such, vitamin D is a potential preventive and alternative cure for CoVID-19 for reasons described in this paper and elsewhere.^[82,83] In a preliminary report by Gilicio^[84] he indicated that insufficient levels of Vitamin D below 30 ng/mL 25OHD was prevalent in diabetic, male and critical patients. Silberstein^[78] indicated that tocilizumab which is an anecdotal drug that offered hope for managing severe CoVID-19 patients through its blocking action on the cytokine storm that causes over production of interleukins specifically IL-6 and IL-5. A cheaper safer and readily available alternative that acts in a similar way to the human immune system is vitamin D. It has been known that inadequate levels of vitamin D increases susceptibility to viral infections.^[85,86,87] Vitamin D which is an oil type vitamin is actually a hormone. It has long been known as essential for the absorption of calcium and phosphorous and has fairly recently been found as an immune booster vitamin. The two major forms of vitamin D are D2 (ergocalciferol) which is mainly man-made and added to food and D3 (cholecalciferol) which can be produced by the skin in the presence of ultraviolet light from the sun.^[88] Both forms can be taken as a dietary supplement. There are a few natural sources of vitamin D which include fatty fish, fish liver oil, and egg yolk. Before the body can use the vitamin D in whatever form it has been taken, it has to be metabolized into its hormone form. In the liver it is converted into 25OHD and in the kidney this gets converted into calcitriol, the active form. In the bloodstream, vitamin D and calcitriol is circulated by vitamin D binding protein.

It is the circulating form of vitamin D, calcitriol, that has been reported to affect the immune system.^[89] In macrophages, the local conversion of 25OHD into calcitriol has been reported to increase cellular immunity by affecting the production of cathelicidin which is an antimicrobial peptide.^[90] A study by Stubbs group indicated that a population of immune cells with increased vitamin D receptors and cathelicidin developed in renal dialysis patients treated with high vitamin D doses.^[91] Adams and Hewison.^[92] wrote that calcitriol

exerts immunomodulatory and anti-proliferative effects. The importance of calcitriol has also been considered for preventive and therapeutic actions in various health conditions including cancer, diabetes, cardiovascular and infectious diseases.^[93,94] In a review of various studies, it was suggested that vitamin D oral dose of 50,000 IU minimized the potential of getting influenza.^[95]

The expression of vitamin D receptors and hydroxylase enzymes by immune cells is a clue for its role in maintaining immune stability and serving as an alternative cure for CoVID-19 that has now affected 210 countries. The research by Griffin *et al.* focused on the effect of vitamin D on the expression of major histocompatibility complex class II (MHC II) and co-stimulatory receptors as well as the differentiation of monocytes to dendritic cells (DCs).^[96] After interception of foreign materials, up-regulation of MHCs/peptides and co-stimulatory ligands on the surface of DCs ensue at which specific T cells are eventually activated. The maturation of DCs which lead to activation of T cells is affected by the components of the pathogens, secretions of the macrophages and parenchymal cells, and contact with the T cells.^[97,98] Studies have indicated that in vitamin D receptor (VDR)-deficient mice, the effects of 1,25OHD and D analogs when absent did not result in attenuation of total DC numbers.^[99] Additionally, VDR mediates functionally important gene expression profile affecting multiple pathways. Griffin *et al.*^[100] suggested that 1,25OHD and VDR mediates a functionally important gene expression profile in human DCs which was also reported by the group of Woltman.^[101] Griffin *et al.* suggested that influences of the 1,25OHD and the VDR pathway on DCs maturation are physiologically distinct and may signify a stronger foundation for immunotherapy than other antigen-presenting cells (APCs) or APCs modifying agents. Also, direct modulation of T cells and macrophages have been exhibited which suggests that the T helper (TH) lymphocyte is the specific cellular target for the immunoinhibitory effects of 1,25OHD.^[102,103] that modulate the immune response. Peripheral blood lymphocyte studies suggested that production of IL-2, tumor necrosis factor- α (TNF- α), and interferon- γ is suppressed by 1,25OHD.^[104]

The body has a built-in mechanism of protecting itself from foreign invaders but the importance of Vitamin D deficiency has appeared to result in increased susceptibility to infection because of its role in maintaining a strongly regulated immune response. This was enhanced by the discovery that: 1) the existence of VDRs deactivated human inflammatory cells.^[105] 2) the 1,25OHD inhibit T cell proliferation^[106] and 3) the capacity of infection-activated macrophages to produce 1,25OHD.^[107] Vitamin D has been reported to participate in both innate and adaptive immunity both of which influence pathogen invasion.^[108] Vitamin D deficiency has been documented in various infectious diseases like tuberculosis.^[109] and the use of 1,25OHD has been

recorded in the monocyte killing of mycobacteria.^[110] but insufficient level of 25OHD inhibits this mechanism.^[111] Many studies linked vitamin D deficiency with diabetes Crohn's disease, mellitus type 1, asthma and multiple sclerosis.^[112,113,114] The non-classical actions of vitamin D are seen in cell proliferation and differentiation and immunologic effects that result in tolerance and protective immunity.^[115] The antigen presenting cells which are the macrophages and dendritic cells (DCs), T cells and B cells, are able to synthesize 1,25OHD, which acts as hormone in an immune event. Ginde *et al.*, reported a study between 1988 to 1994 involving 19,000 subjects which indicated that people with <30ng/mL vitamin D levels were more susceptible to upper respiratory tract infection compared with those having sufficient levels.^[116] Similarly, studies involving upper respiratory tract infections, influenza, HIV and bacterial vaginosis showed that lower vitamin D levels exhibited higher rates of infection.^[117,118,119,120] A study involving a double blinded placebo using nasopharyngeal swab exhibited that administration of a therapeutic dose of vitamin D significantly decreased the prevalence of influenza^[121,122]

Vitamin D nanoemulsion

Various delivery methods to enhance the effectiveness of vitamin D while reducing possible risks have been described^[123,124] Vitamin D supplement is a low- cost practical method to enhance immunity on a daily basis with dietary sources that are available and most countries have fortified various food products. After digestion of food or supplements, vitamin D is mixed with micelles and its absorption require cholesterol transporters in the intestine before it is activated in the liver and kidneys. Its absorption is blocked when there are not enough lipids in the intestine. A study showed that vitamin D in an oil carrier has better oral bioavailability with greater 25OHD response than powder form or ethanol form^[125] The challenges involving vitamin D absorption and bioavailability arise from (i) high hydrophobicity that prevents direct dispersion of the vitamin in an aqueous matrix, (ii) chemical degradation leading to the reduction of functionality and bioavailability, and (iii) variable oral bioavailability.^[126,127] Exposure to light, oxygen and high temperature cause isomerization and degradation into the inactive conformation (Grossman). These challenges must be overcome to harness the immune functions of vitamin D efficiently and cost effectively. Nano particle encapsulation in colloidal dispersion could serve the needs of vitamin D against degradation and inactivation or to make it miscible in aqueous environment. The use of nanotechnology, particularly those which are biocompatible and biodegradable, for such purposes may be the best approach. Nanoencapsulation of vitamin D improves appearance, taste, shelf life and absorption.^[128,129] Various types of colloidal systems including nanoemulsions, liposomes, micelles, as well as solid nanoparticles have been used as delivery carriers for actives in pharmaceuticals.^[130,131]

A novel nano dispersion technology for vitamin D could mimic a bioavailability of 131%.^[132] that was reported for a similar lipid. The use of nanotechnology in the preparation of lipid soluble actives has shown the actives conversion into more absorbable form that has the potential to make it more effective.^[133] The components of the vitamin D nanoemulsion could make it more bioavailable as well as more biocompatible with the human body. Research has indicated that co-administration of vitamin D with lipids increases its bioavailability.^[134] This enhancement in bioavailability could be beneficial to its therapeutic effects. Co-administration of vitamin D with lipids could increase the solubility in the stomach through the formation of micelles that could facilitate the diffusion and absorption.^[135,136] These studies indicated that vitamin D in the presence of lipids could be absorbed into the systemic circulation through the intestinal lymphatic absorption avoiding the hepatic first-pass metabolism.^[137,138] Co-administration of vitamin D with lipids could be done through the use of lipids as carrier or in the form of a nanoemulsion using biodegradable biocompatible nanoparticles.^[139] An emulsion is a colloidal mixture of two types of liquids (i.e. oil and water; water and oil or mixture of oils and water) which are normally immiscible with each other. By using specific surfactants or emulsifiers and co-surfactants, oil and water could coexist in a single phase called emulsion. An emulsion consisting of a water phase and an oil phase plus the emulsifiers and co-emulsifiers makes the colloidal dispersion stable with less surface tension. A nanoemulsion is prepared like an emulsion but is subjected to additional processing to make the particles smaller so that they are nano-in size. The nanoemulsion consists of particles in the 1 to 100 nanometers (or bigger) in diameter.

Nanoemulsion of vitamin D that has been reported in the literature have indicated that the use of nanotechnology improves its bioavailability.^[140,141,142,143] The components of the vitamin D nanoemulsion^[144] could make it more biocompatible with the human body. Nanoemulsion of vitamin D using only biocompatible natural materials^[145] reinforce its potency and increase its bioavailability^[146] while making it more shelf-stable in the absence of harmful synthetics. The benefits of nanoemulsion of vitamin D include miscibility with water, improved biocompatibility, increased absorption, enhanced bioavailability which must be further studied to be quantified, and increased shelf-life due to protection against light. Nanoemulsion of vitamin D with natural materials provides improved solubility by making it miscible with water. It allows for enhanced biocompatibility because of the chosen components of the nanoemulsion that keep vitamin D from rejection and degradation by enzymes or macrophages in the body which makes the vitamin D bioavailable that leads to increased absorption. The embedding of the vitamin D droplets in the nanoemulsion rather than in its natural form protects it from light degradation giving it a better

shelf-life. Making the vitamin D more available and protected from degradation as a nanoemulsion would lead to enhanced bioavailability but this has to be further studied to be quantified.

CONCLUSION

AS CoVID-19 infects more people worldwide it continues to claim lives. Today no drug has been completely tested for the disease and prospective vaccines are still being developed and studied. Meanwhile, various parts of the world have shown positive results using Vitamin D as a possible remedy and preventive measure for viral infection including CoVID-19 because of its immune modulation participation in both the innate and adaptive immunity which influence pathogen invasion. Clinical studies have shown that the overwhelming host immune response to the CoVID-19 that may be responsible for the severity and mortality could be regulated with Vitamin D because of its ability to modulate inflammatory responses during viral infection. Additionally, studies have shown that nanoemulsions of vitamin D are more effective compared with conventional vitamin D. Many elderly severe cases of CoVID-19 have been found with insufficient levels of vitamin D. In the absence of a cure or a vaccine, vitamin D is a safe, inexpensive and readily available potential alternative remedy especially for severe cases that must be tested and administered to CoVID-19 patients. The urgency of this matter should not be ignored especially in the remote areas in poor countries where medical preparedness and financial capability is totally lacking if not completely absent.

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Conflict of Interest

There are no existing conflicts of interest in this project.

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