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RESEARCH ARTICLE

REVIEW ABOUT THERAPEUTIC AND PROPHYLACTIC EFFECTS OF VITAMIN (D AND E) ON SOME RESPIRATORY VIRAL INFECTIONS, AND COVID 19

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Abstract

Oxidative stress associated with almost all viral infections; in other words, inducing immune storm which increase generation of reactive-oxygen species(ROS) that causes damage in small vessels cellular membranes extensively at viral infections durance.Vitamin E considered as one amongmany antioxidants examinedin mice in infections of influenza virus, with a leader position for its ability in blocking oxidative damage by its scavenging activity of free-radical. The phenomenon of Vitamin D multi-directional activity is probablybecause of the existence of theVit. Dreceptors (VDR)sin most human cells of non-skeletal.Also, vit. D able tochange the immunity (acquired and innate) , therefore able to be utilized as preventive, therapeutic adjuvant vaccine, for many viral infections difficultly to treat like influenza virus, and course modulating therapy for oral herpes virus, Epstein bar virus, hepatitis B virus, and some respiratory viruses, like covid 19.Retinoic acid has important role in cell differentiation and growth,where vitamin A partially can regulate viral growth. Retinoidsinfluence many of virus infections in different complex ways i.e., ifvariouslines of cellshave an infectionby the human cytomegalic-virus(hCMV), cells exposure to retinoic acid (RA) encouragesexpression of viral nucleic acid with vulnerability to infection .

Introduction:-

Many viral infections can cause dramatic health and economic problems worldwide, among these infections are influenza infection, Hepatitis B viral infection, some respiratory viral infections, and Ebola viral infection and recently pandemic of new corona virus infection.

Previously vaccinations, and / or anti-viral therapies, used to reduce these problems; recently adjuvants are used to either ameliorate immunity of the patient to fight the infection or reduce complications of oxidative stress accompanying viral infection. This can be done by using Vitamins, like those to be mentioned in this review.

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Metabolism:

Two sources of Vitamin D are recognized either from precursor of 7-dehydrocholesterol to cholecalciferol via radiation of UVB on skin, or from food asergocalciferol (D_2)or cholecalciferol (D_3).Figure (1) illustrates the metabolic pathways for both forms. 25-hydroxylation metabolized to calcidiol (25(OH)D), via liver enzymes CYP27A1 and CYP2R1 (cytochrome P450-linked 25-hydroxylases) and followed then by 1α-hydroxylation to the activity metabolite of 1α,25–di-hydroxy-vitamin D_3 (calcitriol, 1α,25$(OH)_2$D) which catalyzed via cytochrome P450-linked to 25(OH)D(3)-1α-hydroxylase (CYP27B1) which present in kidney, as well as extra-renal tissues such ascells of immunity [1- 3]. Because of a feedback development, the chole- and ergocalciferol metabolism, activation and catabolic reactions are modified significantly. Production of 1α, 25$(OH)_2$D positive regulators are parathormone (PTH), parathyroid secreted hormone, and Ca level, while growth factor-23 of fibroblast (FGF-23)and phosphate level are considered as negative ones. The activity of 1α-hydroxylase is affected by all of them [4].

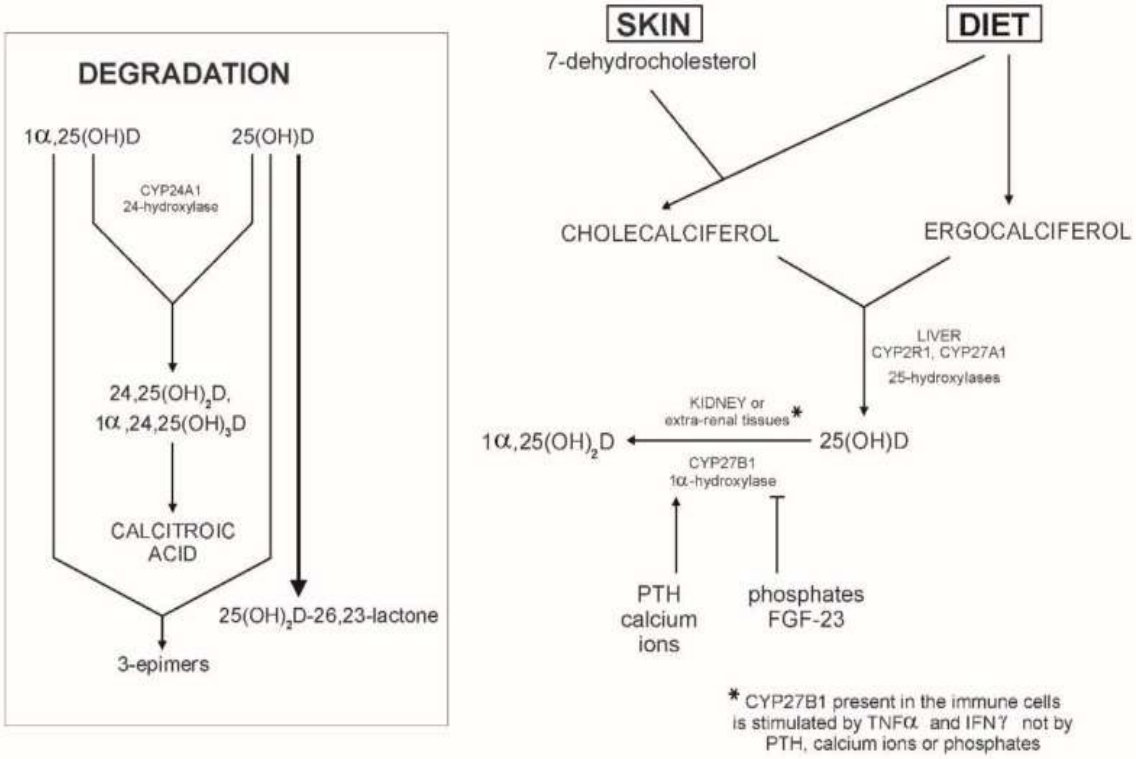

Figure 1:- Vitamin D Metabolic pathways.[5].

CYP27B1exist in the cells of immunity is not regulated viasignaling of PTH, FGF-23, Ca, or phosphate, but cytokines stimulating it i.e.interferon gamma(IFNγ) and tumor necroticfactor alpha(TNF α) [3,6]. In turn, in keratinocytes CYP27B1 is regulated respondingto activation of Toll-like receptor (TLR) and injury [3]. Expression of earlier enzyme (extra-rena)l might beencouragedvia receptors of recognition of alternate pathogen or (PRRs=pathogen-recognizing receptors) [7]. 1α-hydroxylase (the extra-renal type) regulation is dependent highly on circulating 25(OH)D concentration[8].

1α,25(OH)D and metabolites, at bloodstream are transferredviavit. D binding protein carrier (DBP-25(OH)D), and the transporter affinity is higher for 25(OH)D [5]. Degradation of metabolites is catalyzed throughCYP24A1 resulting in 24-hydroxylation with1α,24,25$(OH)_2$D and 24,25$(OH)_2$D formation that are converted to calcitroic acid subsequently [1, 4]. Calcidiolin circulation mightas well changedthrough CYP24A1 to 24, 25$(OH)_2$D(aninactive form)and lactone of 25$(OH)_2$D-26,23- [1].

Three-epimers metabolites are yieldedthroughC-3 epimerization in ring A of 1α,25$(OH)_2$D, 24,25$(OH)_2$D and 25(OH)D, which areslightly weaker in activity biologically than 1α,25$(OH)_2$D. In 1994, theseepimers were stated for the first time in keratinocytes of human [9].

Action of Vit. D (Genomic and Non-genomic):
Pathways of non-genomic and genomic cellular metabolism is affected byVitaminD.Vitamin D,acts mostly viaVDR, and then, after a heterodimer yielding with retinoid X receptor (RXR). The latter dimer entersnuceus, and connects to vitamin D responsive element (VDRE) in genomic nucleic acid to control gene transcription.

Non-genomic pathways are the cell membranes rapid reactions and had been proposed for estrogen,corticosteroids, and thyroid hormone [4,10,11,and 12]. Possibly through a (1α, 25(OH)$_2$D ,membrane-boundreceptor protein that can give fast reply steroid-binding protein, which as wellbeen known as stress protein endoplasmic reticulum 57).Activity of Ca-activated chloride channel and rapid cellular Ca efflux are regulated by vitamin D [12].

Responses(non-genomic) to the metabolite of active vitamin D continue through the phospholipase C systems messenger, protein kinase C and phosphatidyl-inositol-3'-kinase (PI3K), starting signal transduction of Ras/MAPK and Ca gateways widening[7].

Besides the role in bone metabolism and Ca homeostasis, vitamin D causesdifferenteffects in extra-skeletal tissues via the VDR, thatexist in most body tissues [12, 13]. Affinity of VDR for ($K_a = 10^{-10}$ M) 1α,25(OH)$_2$D is higher ifcompared to($K_a = 10^{-8}$ M) 25(OH)D [13]. Activation of receptor is the foundation for 3% human genes regulation. Vitamin D involved inregulatingfunctions of nervous and immune system in addition to cardiovascular, gastrointestinal and skin diseases role, cancer repression, or restraining of autoimmune diseases [4,11].

Recently, it was found that polymorphism in some proteins and enzymes of relation to vitamin D, e.g. DBP, CYP28B1, VDR or CYP24A1 (particularly polymorphs TaqI, FokI, BsmI, andApaI), able to affect the response of individuals to treatment with anti-infectious therapy e.g. interferon/ribavirin in chronic hepatitis C [14,15], individuals susceptibility to tuberculosis, cancer, disease of Crohn, and ulcerative colitis or the increasingT1DM risk, as was noticed in people of European origin [16,17,18,19].

Serum Concentrations Guidance:
Vit. D status of the bodydepends on the serum 25(OH)D levels, sinceit's relatively to DBP hashigh affinity and of 25 days as the half-life . Assessment of 1α,25(OH)$_2$D in the bodyto define level of vitamin D is not advisable, as its serum half-life is only a some hours (ca. 7 h) [10,13]. 25(OH)D serum concentration, that indicates vit.Davailable in sufficient level for organism, is (ca. 75–200 nM/L) or 30–80 ng/mL.A strong deficiency of vit. D is whenconcentrations are less than10 ng/mL [13,20,21,22,23,24].

Vit. D anti- infectionagent:
Functions of Vit. D forsystem of immunityisnot easy to identifysince the immunity response is not constant and relies on stage of infection.

VDR detected in cells of immunitypropose that vit. D is one of the organizers of immune system.Activated B and T cells in vitroas wellas the cells of epitheliumthat line the lower and upper tract of respirationable of transforming25(OH)D (inactive metabolite) into 1α,25(OH)$_2$D(which is metabolically active). Thelatter metabolite affects cells of immunity inparacrine way or an autocrine,intracrine(for example,via insidepathways of cells) [25-27].

Vit. D probable role in diseases of infectionsis illustratedthrough its effect on the adaptive and innate immunity (Figure 2):

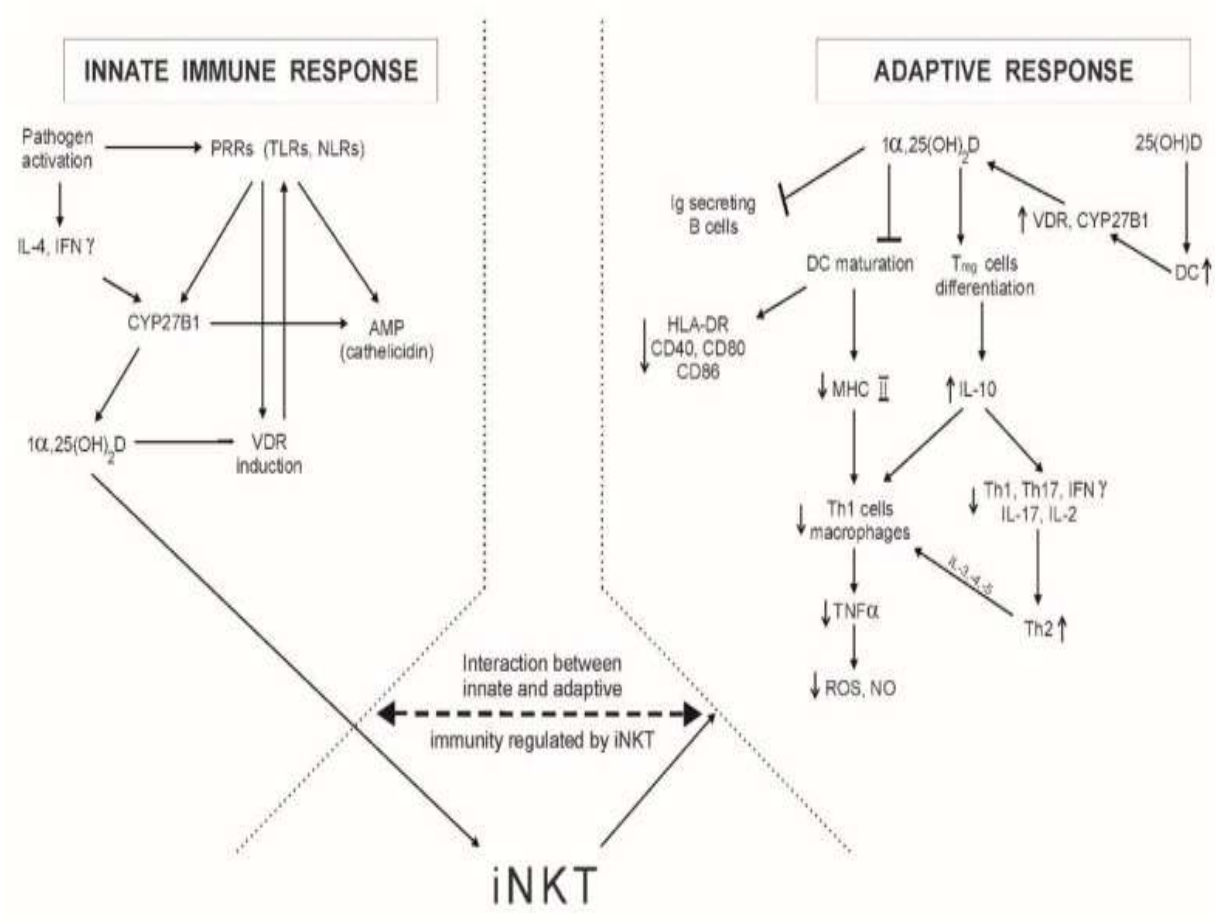

Figure 2:- Vit. D role in the immune response.[5].

Innate Immunity and Vit. D:

Pathogen Recognizing Receptors (PRR)s:

Generally, innate immune response or nonspecific, was proved to be the first defense line against agents of infection and initiates presentation of antigen [28, 29].

Innate immunity response crucial points are the receptors of Toll-like (TLRs), which are of differentsubgroups of innate intracellular PRRs thatexistatmonocytes, cells of epithelia, poly-morpho-nuclear cell, and macrophages. TLRs can recognize compounds of pathogen origin; e.g., bacterial, viral lipopolysaccharides, proteins and nucleic acid. Cytokines released by activated TLRs would induce antimicrobial peptides (AMPs), ROS,defensins, and cathelicidins [3,6,7, 25,26]. VDR induction affected or affect by numerousTLRs e.g.co-stimulatory molecule CD-14, co-receptor expression for TLR4, that is triggeredvia $1\alpha,25(OH)_2D$ in epidermal keratinocytes and monocytes. In macrophages, CYP27B1increased expression considered as indirect AMPs result, thatencourages TLR2 [6].It had been shown byGreiller and Martineau that in macrophages [7], heterodimer of TLR2/1 ligation causes CYP27B1up-regulation, in a similar manner to the TLR4 by lipopolysaccharide (LPS) or TLR8 by CL097 ligation.

Production ofCYP27B1 byTLR ligation is probably occurs if alternate PRRs or TLRs encourageenzyme (extra-renal) activation, permitting calcitriol to causeeffects more extensively on the immunity response [7]. In case of infection by virus, pathogen-associated molecular patterns(PAMPs) mightidentified by different PRRs, e.g. nucleotide binding-oligomerizationreceptors domain (NOD)-like ligand (NLRs) and retinoic-acid-inducible receptors of gene-I (RIG-I)-like ligand. In epithelial cells and myeloid, 1α, $25(OH)_2D$ encouraged the receptor of NOD2through2 VDREs in NOD2gene. Products of lysosomal breakdown (peptidoglycan of bacteria), if associated with calcitriol, it would induce NOD2 to enhance signaling of AMP and expression of beta defensin 2 [7, 30].
Interleukins (IL) IL-1β, TNFα and -6, and -12 and other inflammatory cytokines are yielded at an innate immune response early phase. Among others, cytokines encourageproteins of acute phase synthesis and contribute to the

cells activation and recruitment of the response of adaptive immunity. Signaling of PRR also contribute to the chemokine ligands (CXCLs) production of e.g. IL-15 and CXCL8–CXCL10 thatstimulate production ofnatural killer cells (NK) and neutrophils which have role, particularly in immunity (innate) versusbacteria [7].

TLRs up-regulation can occur by other ways. Neutrophilsdon't synthesize1α-hydroxylase but, express the VDR unlike macrophages. Hence, in these cells, it is hard to induce 25(OH)D transformation into the functioning compoundviaTLR stimulation. Proteins of surface, e.g. transforming growth factor β (TGFβ), or triggering receptor on myeloid cells-1 (TREM-1) , exist on the epithelial keratinocytes or neutrophils, respectively, mightassociate in response of cell to serum 1α,25$(OH)_2$D by CYP27B1 expression stimulation, through TGFβ or signaling of TLR, through TREM-1, [30]. TGFβ able toassociate with calcitriol to yield 5-lipooxygenase (5-LO) that stimulates the leukotrienesproduction andchemicals that associate with the bacteria phagocytosis [30].

Pathogens destruction is aresponse ofmany of antibacterial innate immunityvia autophagy [27]. Chun et al. [30], suggestedsuch process which is significant for the antimicrobial response that triggered by vit. D against infection ofMycobacterium tuberculum **.**

AMPs released by TLRhave wide- spectrumantiviral and microbial effect, and proved to inactivate viral influenza [25]. The AMPs antiviral effect is resulting fromenvelope proteins destruction performed via cathelicidins. As for antibacterial impacts, AMPs, cause disruption of microbialmembrane. Cathelicidin 37-residue in humans, as active antimicrobial along withLL-37helical peptide, amphipathic, is cleaved from the pro-peptide , human cathelicidin (hCAP18). The cathelicidin majority is kept in vesicles of neutrophil as well as other kinds of immunity cells, as B lymphocytes and NK and monocytes that are able to express hCAP18 [3]. In vitro, 1α, 25$(OH)_2$D and vitamin D active metabolite stimulatecathelicidins production in human macrophages throughelevated VDR expression [26]. Sundaram and Coleman [26], mentioned that VDRE up-regulation via TLRs causecathelicidin transcription that destroys intracellular Mycobacterium tuberculosis. Szymczak and Pawliczak [27], revealed that hCAP18 has activity against viruses and bacteria. In case of infection by virus, the cells of lung epithelium are able to convertecalcidiol into the calcitriol as active metabolite, causing an increase inproduction of hCAP18. Beard et al. [3] showed thatexpression of cathelicidin in keratinocytes and macrophages is encouraged by CYP27B1, and when there is no VDR, CYP27B1, or 25(OH)D, the capacity of cells to yieldcathelicidins is highly disrupted. Report of Pawliczak and Szymczak [27]showed that not only signaling of TLR is contributing, yet cytokines also do so, e.g. IL-4 and IFNγ might affect CYP27B1production. IFNγexistence encouragesCYP27B1 of macrophage. 1α,25$(OH)_2$D has role in the down feedback strategy which inhibits TLRs hyper-activation [27].

1α,25$(OH)_2$D effect on synthesis of cytokine by stimulation of viral pattern recognition receptor differs amongpathogens. Fitch et al. [31] mentioned thatvitamin Ddid not succeedin modifyingvirus or TLR7/8- of syncytial respiratory (RSV) toenhanceproduction of cytokine of innate immunity, evenat high concentrations (supra-physiologic) levels.

Anti-Microbe -Proteins or Peptides (AMP)s:

AMPs are organized byVitamin D, e.g. defensins. 1α,25$(OH)_2$D stimulates modestly human beta defensin 2 and the effect of the latter as antiviral comes from its ability as chemo-attractive for monocytes and neutrophils [3, 26]. Nevertheless, concentration of 25(OH)D serum was not associated with AMPs serum levels in pneumonia of community-acquired origin[26].

Analysis of human nucleic acid revealed that there is VDRE incathelicidin andbeta defensing promoters. Transcription of Cathelicidin only seemed to beinduced in monocytes via 1α,25$(OH)_2$D [30]. The elevated beta defensin 2level is a result from the interleukin-1 (IL-1) and 1α,25$(OH)_2$D decreased expression in monocytesAMPs for gene induction, VDRE needs to integrate with nuclear- factor kappaB (NFκB) in thepromoter [30].

Adaptive Immunity and Vitamin D:

T- Lymphocytes:

Response of adaptive basis is: presentation of antigen to cells of T and B type, where antigen-stimulated production of antibodies, cytokines, chemokines, hormones, and enzymes of a wide spectrum will occur. The existence of VDR in the activated lymphocytes was first to be noticed to correlatevit. D role with system of immunity [30].

Subgroups of T cells are few kinds of cells:cells of $CD8^+$ T showvitamin D-activating 1α-hydroxylase and VDR at high levels relatively; cells of $CD4^+$ T; cells of memory; and cells of NK. Activated cells of $CD8^+$ T able

todifferentiate to cytotoxic (CTLs), importantagainst cancer and intracellular pathogens. Activated cells of $CD4^+$ T able to differentiate to cells of Th cells, cellsof regulatory (T-reg) (cells of suppressor)type, Th17, and γδT cells, Th2, Th1, and Th9cells thatyieldvariouscytokines profiles. Thus interferon γ, IL-2, and TNFα produced from Th1 cells, whileIL-3, -4, -5, -10, and -13 secreted from Th2. cytokines induced- CD+4 T cells give enforcement to other cells of immunity, e.g. CTLs, and to the response of antibody in circulation, by CD40:CD40 bond of antigen-specific B cells co-stimulatory sites[6,26,27,28,30,32]. Th cells role involve: immunoglobulin production enhancement, activation of macrophage, and mastocytes(Th2) and eosinophilsgeneration [28]. Response of stimulated Th1- is the main factor for variousviral and bacterial infections whereaswhen thisprocess becomes not controlled, it causes autoimmunity [29].

Regardingvit. D role in response of immunity, itbehaves likeTh cell generation modulator and changingproduction of cytokine type , as well asbyT-reg cells promotion, that are related to anti-inflammatory reply , immune suppression, and for limitation processes of inflammation [29]. One report concentrated on25(OH)D ability for stimulatingT-regcells viathe cells for antigen presentation (dendritic cell (DC))induction to synthesizeCYP27B1 and VDR [33]. Jeffrey et al. [33] reported the vitamin D significant form forcells T-reggeneration was non-25(OH)D DBP-bound. Areport by Bruce et al. [29] showed that $1\alpha,25(OH)_2D$ able to regulate cells of invariant NK T (iNKT), that are able tobehaveasorganizer cells and associate in the relation between adaptive immunity and innate. Induction of iNKThadproven protection against autoimmunitydiseases. A report of Sigmundsdottir et al. [34] mention that chemokine expression of receptor 10 (CCR10) by$1\alpha,25(OH)_2D$- on cells of T-lymphocyte eases associationwithcells of competent immunity, e.g.detecting keratinocytes CCL27 . In vitro,$1\alpha,25(OH)_2D$,blocks Th1 cytokines expression and stimulates cytokines of Th2. Cells of Thsubgroups;forexample,cellsof Th17, secrete IL-17, have important role in autoimmunity [6, 30].

Inverse relationships between activity of disease and concentrations of vitamin D in patients with T1DM, disease of inflammatory bowel, autoimmune thyroiditis, arthritis (rheumatoid), or multiple sclerosis had been noticed [35].

$1\alpha,25(OH)_2D$ seemed to reduceautoimmune process viablocking activity of Th17 cell [36]. $1\alpha,25(OH)_2D$ can reduce the antigens presentation ability via DC maturation inhibition. A decrease in the molecules of co-stimulatory receptors and human leukocyte antigen HLA-DR expression i.e. CD40, CD86, and CD80 were observed. $1\alpha,25(OH)_2D$ triggers T-regdifferentiation that induces production of IL-10 which inhibitsIL-12. $1\alpha,25(OH)_2D$-treated DC showed less co-stimulatory MHC (major complex of histocompatibility) II binding, compared to intact ones[29]. Based on that, production of macrophage and cells of Th1 is diminished, yet the cells ability for inducingT-reg is conserved [6, 26,29]. IL-10 induced as wellblocks Th17cells and Th1 and soIL-17, IL-2 and IFNγproduction leads to tolerance of immunity [6]. The foregoingrenderscells of Th2 to be predominant. Accordingly, the enhanced IL-4, -5 secretion, and -13 morereduce Th1. In vitro, inmonocytes of human, $1\alpha,25(OH)_2D$ was proved to be Th1 cell- cytokines mediated inhibitor as well as for(TNFα), but incase of mice, in vivo as Th17 suppressor viaIL-23 and -6 down-regulation [6,26,29]. Bruce et al. [29], showed that naïve $CD4^+$ Th cells incubated with$1\alpha,25(OH)_2D$,throughpriming of Th17 cells, it wouldblock production of IL-17. Chun et al. [30] illustrated thatexpression of DC gene can be organizedvia 2vitamin D major metabolites: $1\alpha,25(OH)_2D$ and 25(OH)D , considering this as a different way for immunomodulation.

According tostudies of animals, it was proposed that Th2 cells progression might have exacerbating effects on diseases of allergye.g.dermatitis, asthma atopiabyinflammatory processes induction [6]. The increased Th2 cytokines production (IL-4, -5, -13)noticed in the atopic dermatitis acute period, leads to cathelicidin suppression and infection vulnerabilityincrement. In the disease chronic phase, Th1 cells were ofpredominance [6].

ViaIFNγinhibiting, $1\alpha,25(OH)_2D$ blocks stimulation of ROS and production of nitric oxide. All effects, with IL-17 suppression are the causes for the decreased pathogens resistance e.g. Citrobacter**a**ndToxoplasma [6, 37,38]. Report of Ehrchen et al. [37] proved that mice VDR-knock outingleads to change in response of Th1 to infection with Leishmania major, thoughIFNγ produced via$CD8^+$ and $CD4^+$ Th cells.Rajapakse et al. [38] noticedIL-12 and IFNγreduction levels in infected micewithToxoplasma gondii, suggestingTh1 cell blocking. After$1\alpha,25(OH)_2D$ treatment, $CD4^+$ Thcells counts,splenocytesreducedwith obvious apoptosis were noticed. Report of Ryz et al. [39] revealed reduction in Th17 cells of infected mice with Citrobacterrodentium when $1\alpha,25(OH)_2D$ is given. Based onTh17impaired response, production defect in antimicrobial peptide REG3γ was observed.

1α, 25(OH)$_2$D leads to antigen-presentation and T-cell stimulation ability of macrophages and monocytes and CD40, -80, -86, and MHC II reduction. Activation of NFκB by 1α,25(OH)$_2$D contributes to IL-23 and IL-12 suppression that are linked to differentiation of Th1. [7,29].

T cell responses regulation is viaDC existence and vitamin D inactive metabolite such as 25(OH)D. Jeffery et al. [33], described upon maturation,CYP27B1 is produced by DC if come in contact with LPS or T cell resulting in the 1α,25(OH)$_2$D release and synthesis that affects responses of T cell.

B-Lymphocyte s:
1α,25(OH)$_2$D considered to be generation inhibitor and actsin vitro as anagent of pro-apoptosis in B cells (activated). Despite it does not generate thesecells;yet it act as differentiation inhibiter [26]. Fang et al. stated that in mice having virus of influenza (primary infection),and inducing immune protection, meaning a significantdependance on existence oflymphocytes B [40].

1α,25(OH)$_2$D suppression effects were observed refereeing to secreting B cells of immunoglobulin (Ig). 1α,25(OH)$_2$D was particularlyblocks theirprogression after mitogenicstimulation [41]. Ig mechanism impact is not one only for interaction B cell and vitamin D. 1α,25(OH)$_2$D regulatecells of B viaCCR-10 and IL-10 [42]. Heine et al. [43], reported that B cells through activation viasignals of IL-4 and CD40 receptor, illustrateelevatedgene expression for 25(OH)D 1α-hydroxylase CYP1α, then viasignificant 1α,25(OH)$_2$D amounts production. In B cells, expression of IL-10 1α,25(OH)$_2$D enhancedthrough VDR transcriptional activity or byCa signaling modulation. Accordingly, it might be proposed that vit. D and 25(OH)D inactive metabolites able as well to modulate the response of immunity.

Vitamin D Anti-Inflammatory Action:
Vitamin D behaves byfeedback loop promotion to blockinflammatory events and antibacterial processes over activity through TLR4 and TLR2 down regulation in monocytes [26, 30]. 1α,25(OH)$_2$D was stated to reducepro-inflammatory chemokine production in cells of epithelium of human respiratory system and down regulate cytokines such asTNFα, IL-6, and IL-8, in vitro within various cells [26].In respect tolymphocytes of human, vitamin D anti-inflammatory effect occurs through inhibition of NFκB. This factor of transcription regulates genes expression encoding for proteins of immunity yieldedin infection, e.g.proteins of acute phase, chemokines, and cytokines or enzymes of inducible effectors [6, 26].

Proliferation of T-cell considered as Vitamin D-modulated wherethe mechanisms partially lead to responses of anti-inflammatory throughelevation ofT cells subgroup proliferation, CD8α. Cells of T type, unlike cells of $CD8^+$ T, considered of no cytotoxicity, rathermighthave a role in gastro-inflammation suppressing [30].

Time-Dependencey of Vitamin D Immuno-modulatory Effects:
Vitamin D immune-modulatory effects areassociated to infection (late or early periods). The association levels in circulationfor 25(OH)D and α_1-antichymotrypsin , in tuberculosis, protein of an acute-phase was illness- correlated, and not with the response of early acute-phase of infection [46]. Also, 1α,25(OH)$_2$D interacted differently with various mechanisms stated to account on time in human cells leukemia.Report ofTse et al. [47] stated dependency of time forNFκB in HL-60 cells biphasic regulation. After HL-60 cells exposure to 1α,25(OH)$_2$D, suppression in first 4h ca. with a late(8–72h)prolonged - NFκBtranscription factor reactivation.With this stimulation, there weregenes of anti-apoptotic and inflammatory up-regulation e.g.IL-1β, Bcl-xLand TNFα [47]. This effect has indirect impact on the regulation of immunityillustratedvia vitamin D since the processes of inflammation are related highly to the cells immune response to pathogens. Sundaram and Coleman [26],proposed that in vivo study, the response of immunityin mice to allergens suggested that supplementation of (1α,25(OH)$_2$D by injection of 100 ng) appliedfollowingprimary sensitization period blockedlocal inflammatory response and eosinophils at high levels in lung tissues and bronchoalveolar lavage fluid. But this effect couldn'tbe seeninevery day-supplementation throughout that study.

RetinoidsRole in Influenza Symptoms and Pathogenesis:
Influenza A epidemiologic observations and seasonality are due to wide population- impairing immunity ofinnate typeattributed to a reductionin sunlight exposure atwinter months and a consequent vitamin D deficiency [48–50]. Theory of Cannell proposed that epidemics of influenza are consequent of disease dormancy which is activatedresponding to deficiency of vit. D.

VitaminsD and A have intermingling roles in influenza and retinoids have indirect role in pathogenesis of influenza infection. For example, radiation of sun has differentimpact on vit.D and A; i.e. reduces Vit. A,yetelevates vit. D.Vitamin A and D can inhibit one the other. Retinoids can regulate growth ofepithelial cell of airways, gene expression, andprogression.Influenzasymptoms are identical to toxicity of retinoid. pharmacological and/or supplementary levels induce symptoms of influenza-like.They also partially organize the activity of virus. Theyaffect block or stimulation ofpathogenesis of influenza.

Sunlight reduction, and/or deficiency of vit. D elevatessimultaneously accumulation, expression, and endogenous retinoidstoxicity potentials (such asreductionin the vit. D-to-vit. A ratio), thatagitate activation of virus or elevatesusceptibility of host to influenza virus (novel strains). Moreover, during normal retinoid physiological concentrations seem to functionalong wiothvitamin D to blockpathogenesis of influenza, higher concentrations with (very low vit.D: A ratios) make it wors and mightencouragefatal disease or severe complications. Influenza infections outcome mightpartially relies onbalance ofthe ratio amongvitamins concentrations.Vit.A and Vit. D roles in influenza may extend to genetic variability in their metabolism and their levels [51].

Retinoids:

Retinoid as synthetic and natural congeners,are basicallysignaling molecules of fat-soluble dietary-derived principally liver stored and are necessary for development of embryo, normal homeostasis of cell, differentiation of tissue,secretion of mucus, and growth [52, 53]. Vitamin A active form (Retinoic acid) in most systems' cellulardifferentiationconnected to and activates receptors(retinoid X receptors (RXRs)), (retinoic acid receptors (RARs); that regulate many target genestranscription [54–56].

RXRs and RARs are lipophilic thyroid / steroid super-family members of factors of ligand-dependent nuclear transcription agentswhich composed ofretinoids, steroids, vitamin D_3 and thyroid hormones. Since they are able todiffuse readily from the source and permeatingthe target, hormones of lipophilic property are of organization potentials for development, cell differentiation, and organ functions [68, 69]. The RXRs and RARs present in3products of identifiable gene— β, γ, and α. Atactivation of ligand, the function of receptors as factors of hetero-dimeric transcription and control the target genes expression viaconnecting to specific sequences of DNA, termed of RA -elements respond (RAREs) [57, 58].

Free retinol yield retinoic acid viaretinyl esters hydrolysis,liver stored, and retinol release into circulation and transport to tissues of the target, then bound toretinol-binding peptide (RBP). First, through an alcohol dehydrogenase, to retinaldehyderetinol is oxidized and then synthesis of primarily RA from retinaldehyde within the cell microsomes by the dehydrogenase of retinaldehyde occurs. A level of retinol in circulation stays fixed because of a carefull transport system of regulation and ensures target tissues to receive retinol essentialquantity in spite oflarge fluctuations in intake of diet [59]. Many factors of transcription action are influenced by retinoic acid e.g. AP-1 activation repressing viablocking the c-fos and c-Jun induction [60]. Other nuclear receptors are regulated e.g. receptor of vitamin D, peroxisome proliferation-activereceptors (PPARs), receptor X of farnesoid, and receptor X of liver that hetero-dimerizesalong RXR and regulates the transcription factors activation e.g.STAT-1, NF-κB, and AP-1 [56]. RA shows negative effects on growth of cell byRARs alternative activation versus PPARβδ [61].

Retinoic acids at low concentrations arenecessaryfactors of growth for specifickinds of cells, whereasconcentrations of higher level blockgrowth of cell and are teratogenic, cytotoxic, and mutagenic. Toxicity of exogenous vit. A may take placebecause of excessive consumption of diet or from retinoidstreatments. Even though toxicity of vit. A from pro-vitamin A,but carotenoid of plant as sources has never mentioned.Storage in liver, absorption from fortified foods, supplements, and animal foods inretinyl esters form may causehypervitaminosis A. Retinoid intoxication endogenouslymightnaturally take place at cholestasis, ifmetabolites of vit. A are refluxingto bloodfrom liver [62].

Throughout life, retinoic acid is needed for lung alveoli maintenance and a deficiency resulting inalveoli loss and to emphysema features. Alveolar regeneration is induced by exogenous retinoic acid has been stated in emphysema experiment of rat model.Alveologenesis disruption occurs by action of (disulfiram), a retinoic acid synthesis inhibitor. [63].

Circulating retinol= (1–3 μmol/L as normal) doesn'tgive an idea about liverconcentrations forvit. A , because the RBP secreted is controlledhomeostaticly. Hence,concentrations of retinol in plasmadiffer a bitin spite of major

intake alterations in vit. A. Hypervitaminosis A may be seeneven if serum retinol within limits of normality, mentioning that plasma retinol at toxicity conditionsis not anaccurateevaluation of status of vit.A [64, 65].

Vit. A is one of the antioxidant vitamins and its supplements are available as measures for protecting human from disease widely. A review in Cochrane,mentioned the antioxidant effectson mortality (including vit. A), according totrials of randomization, Bjelakovicet al. [66] also went over all trials of randomization where adults consuming singly or combined Se, beta-carotene, and vit. A, C, E.Sixty eight trials randomlystudied with 232,606 cases. When antioxidant trials of supplements were analyzed, no significant effectsfor mortality were noticed (RR: 1.02; 95% CI: 0.98–1.06). Nevertheless, analyzingmulti-variate regression illustrated that, in "low bias" trials as better designed, β-carotene was correlated of significant risk 7% increasing, vit. A 16% risk increasing, and vit. E 4% mortality risk increasing.Vit. C and Se are of no significant effect. Reaserchers arrived to a conclusion that vit. A, vitamin E, and β-carotene treatments mightelevate mortality.

Below are a summary for many evidence lines supporting the model proposed:
1. Vit. A is ofphoto-oxidation sensitivity.
2. Vit. A andD are associated inversely wherevit. A can blockvit. D actions and vice versa.
3. Retinol,major metabolite for retinoic acid hasnecessary role in growth of epithelial cell of airway regulation, progression, and gene expression.
4. Clinical features of influenza simulatetoxicity of retinoid i.e.syndrome of retinoic acid induced through synthetic retinoidsusage for acute promyelocytic leukemia treatment.
5. Vit. A Supplementationable to induce symptoms of influenza-like.

Generally, activity of virus is ofretinoidsregulation.

Retinoidshave an influence to mechanisms and elements which both contribute and blockpathogenesis of influenza.[66]

Influenza virus infection and Vitamin E:
Oxidative stress in organism infected with virus of influenza producesaturated lipid chains oxidation of cytoplasmic membrane (lipid peroxidation), thatminimizes membranes permeability. Atdeficiency of antioxidant,ifmembranes damaged and/or exposed, influenza infection proceeds atstrong pathology and lead tobody serious damage at all levels.

Throughoutinfection of influenza in mice, antioxidant enzymes activity catalase and SOD were modified, besides a reductionon the endogenous antioxidants quantity of low-molecular-weight e.g. ascorbate, α-tocopherol (Table 1) and glutathione. Vit. E endogenic levels were decreased significantly in lung, blood plasma and liver. Moreover,cytochromes modifications were noticed alonga reduction in activities of hepaticcytochrome P-450-dependent mono-oxygenases. Along with the abovementioned, in the disease course, the organism's antioxidant protection buffering capacity is diminished [67].

Table 1:- Endogenous vit. E content [nmol/mg protein] in blood plasma,lung, liver of mice experimentally with virus of influenza A/Aichi/2/68 H3N2 (1.5 MLD50) infected. Values =(means ± SEM) [41].

Group	Lung		Liver		Blood plasma	
	5^{th} day	7^{th} day	5^{th} day	7^{th} day	5^{th} day	7^{th} day
I Control	2.2 ± 0.31	2.14 ± 0.26	4.94 ± 0.51	5.4 ± 0.42	1.8 ± 0.065	1.72 ± 0.07
II Flu	1.47 ± 0.14	1.7 ± 0.17	3.35 ± 0.42	3.12 ± 0.37	1.46 ± 0.035	1.2 ± 0.37

The aboveinformationshows that, during influenza infection virus, a reduction in antioxidant of natural vit. E was observed along with anelevation ofproducts of endogenous lipid peroxidation significantly.
In humans factor of nuclear (erythroid-derived 2)-like 2 (NRF2) encoded viagene NSF2, is regulating protein forantioxidant proteins expression whichhave a role against triggered oxidative damage throughinflammation and injury. NRF2 can control the induced and basal response of antioxidant element-dependent expression of genes for regulatingpatho-physiological and physiological outcomes of exposure to oxidant. NRF2 is ofa significant impact on toxicity and oxidative stress, organizingthe defense byantioxidant [67].

NRF2 can controlpathway of antioxidant andconsidered as pivotal for lungs protection against influenza virus development, injury and inflammation of infection-induced pulmonary under oxidative stress conditions. The antioxidant system of NRF2-mediated is necessary to save the lungs from oxidative storm and injury induced viaviralinfluenza. [67].

Since there is animportantoxidative stress role in viralinfluenza pathogenesis, enormous work had employed to examine the antioxidants influence on influenza course. Pathway of NRF2 stimulated by drugs isexamined for diseases treatment of oxidative stress andinfective influenza virus. In vivo models experiments, in mice predominantly, have animportant place in such studies.

α-tocopherol (vitamin E) is an antioxidants examined against infections of influenza virus in mice,it is alsoof leading position since its impact in blocking damage of oxidation via its scavenging activity of ROS [67].

NRF2 protein expression is noticed to beelevated in vit. E-supplemented rabbits and cholesterol-fed byNRF2activation pathway, leading to induction of manygenes of antioxidant. Vit.Eseemed to stimulate the NRF2protection effect. Furthermore, it was observed that vit. E blocks suppression of NRF2 via allergens in macrophages of alveoli, showed in vivo for asthmatic cases [67].

Clearly the above informationproves the antioxidants role e.g.vit. E, thatable to be shown in differentmethods:

1. Capturing free radicals in multiplemechanism(s) (non-enzymatic or enzymatic).
2. ROS Generation suppression.
3. Indirectly affecting the above processes i.e. by viral replication inhibition.

Sincevit. E is a substance soluble inlipid withhydrophobic terminus; it accumulation within the membranes interior lipid where it behaves as the mainsignificantseries-breaker, as it reacts with lipid radicals (peroxyl)almost4 times faster compared to theirreaction with adjacent side chains of fatty acids. It is famous that vit. E canblock oxidative damage, since its lipophilic property contributes to easy diffusion passively via the membranes of cell, permittingreticulum (single-plated) and mitochondrial arrival.Vit. E saves them against damage and lipid peroxidation (Figure 3). Particularlysignificant is its chain –freeradicals reaction termination thatsaves fatty (multi–unsaturated) acids of the membrane against oxidation ROS[67].

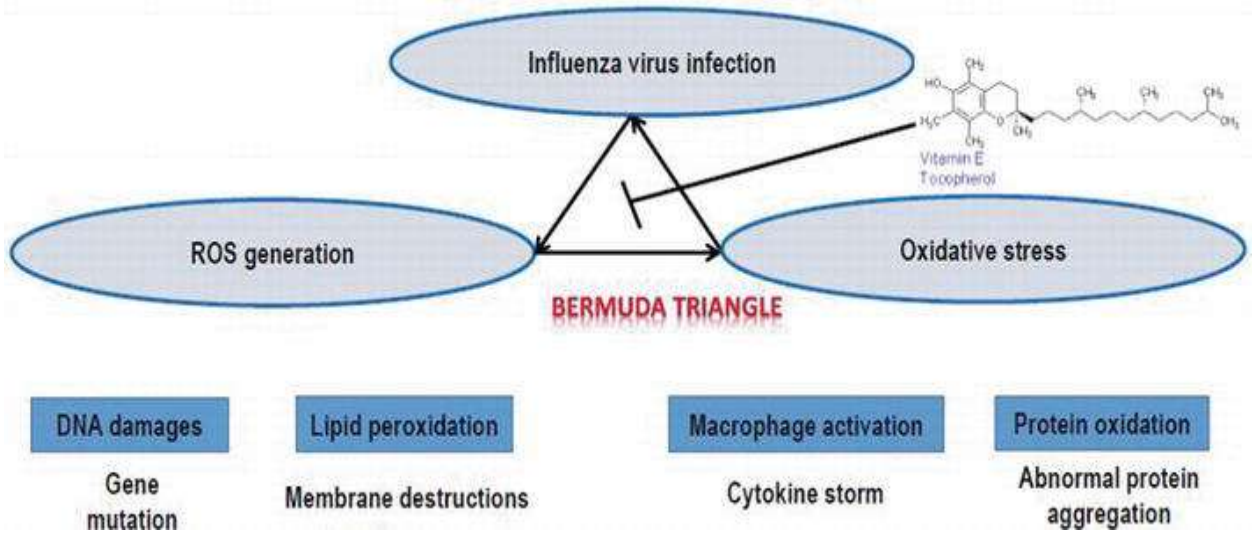

Figure 3:- "Triangle of Bermuda" made by the viralinfluenza pathogenesis in the infested patient. Vit. E action is steered to the core of tempest.[67].

Vit. E affect immuneresponses in various tissues e.g. respiratory system, throughoxidative stress quenching directly, andbyeicosanoid oxidative modulation pathways and synthesis of prostaglandin , inflammatory mediators inhibition, and apoptotic signaling control of lipid. Vit. E stabilizes phospholipids of membranes [67] (Figure 3).

Manyfunctions (non-antioxidant) of vit.E might be necessary for the cell integrity functions and maintenance, e.g. its anti-phospholipase A2 agent function as lipid bi-layer stabilizer of membranes against oxidized and hydrolyzed lipids [67].

Corona virus 19 (covid 19):

COVID-19 was classified by (WHO) as a β CoV of group 2B [68]. Ten COVID-19 genome sequences weretaken from 9patientsof 99.98% identity sequence [69]. Another study showed there was 99.8–99.9% nucleotide identity in isolates from five patients and results of sequence proved the new beta-CoV strain existence [70]. The COVID-19 genetic sequence revealed more than identity of 50% to the MERS-CoVand 80% to SARS-CoV[69, 70], whereMERS-CoV and SARS-CoVinitialized inbats [71]. Hence, phylogenetic evidence analysis indicates the belonging of COVID-19 tobetacorona virus genus that includes SARS-CoV, that infects bats, wild animals and humans [72].

The receptor binding ishost expressed cells which considered as firstinfection step of viral thenfusion followed with the membrane of cell. It is reasoned that the cells of lung epithelia are the viralprimary target. Thus, it has been reported that SARS-CoVhuman-to-human transmissions occurs by the binding between the receptor-binding domain of virus spikes and the cellular receptor which has been identified as receptor of angiotensin-converting enzyme 2 (ACE2) [73, 74]. Importantly, sequence of the receptor-binding domain of COVID-19 spikes is identicalto SARS-CoV. This data effectively suggests that entry into the host cells is most likely via the ACE2 receptor [73].

COVID-19 infected patients presented higher numbers of leukocyte, findings of abnormal respiratory, and plasma cytokines (pro-inflammatory) enhancement levels. Case report of COVID-19 indicated at the 5th day, patientshowed fever, breathing of coarse sounds, a cough, for both lungs, and 39.0 °C temperature. The sputum of patient withpolymerase chain reaction (real-time), resulting aspositive for COVID-19, confirmed infection [75]. Studies of laboratory revealed leukocyte with leucopenia counts of $2.91 \times 10^{\wedge}9$ cells/L whereneutrophils of 70.0%. Furthermore, 16.16 mg/L for a protein in blood, (C-reactive)was noticed that is above the range of (0–10 mg/Las normal). High D-dimer and ESR were observed as well[75]. The main infection COVID-19 pathogenesis as respiratory system for virus targeting was associated with severe RNAaemia, pneumonia, along with the incidence of ground-glass opacities, and injury of cardiaacutely [76]. Significant high blood cytokines and chemokineslevels were observed in cases with infection of COVID-19 includingIL10, IL1RA, IL7, IL1-β, IL8, IL9, basic GCSF, FGF2, IFNγ, GMCSF, IP10, MIP1α, MIP1β, MCP1, PDGFB, VEGFA, and TNFα. Fewcases of great severity admitted to the ICUpresented high pro-inflammatory cytokines levels i.e.IL7, IL2, GCSF, IL10, MCP1, TNFα, IP10, MIP1α, that are due toseverity progression of the disease [76].

Conclusion:-

Because of the above mentioned great and vast effects of vitamin D on immune system in many diseases , and vitamin E effects on immune system specially on respiratory system during infections, it is better to boost immunity of patients with those 2 vitamins, and ameliorate the over stimulation of inflammatory response with its dramatic derangement on patient's life and health.

As the Globe nowadays is passing through the most vicious pandemic of covid 19, causing paralysis of economy worldwide, taking lives of thousands of humans, spreading horror within nations, burdens financial efforts to overcome this tragedy; so it's recommended to

1. give a high single bolus dose of vitamin D (600 000 IU), (this because vitamin D act as hormone in the body and its receptors number would decline if exposed to this hormone for long period(if given as daily maintenance therapy), so it's better to give it as high single bolus dose, every few months to allow for its receptor to get up-regulated), and give maintenance dose of vitamin E and C, with trace amount of Iron and Zinc (because of being the metallic portion of many cytochromes), and used as usual regimen in all health centers worldwide to be given for all populations at the beginning of each cold seasons, as a preventive measure.
2. As for therapeutic measures for covid 19, give high single dose of Vitamin D3 (600 000 IU), as immune-modulator, with high daily dose of vitamin E and C (as antioxidants, because ROS can act as strong chemo-attractants leading to exaggerated immune response, which was observed in patients with COVID -19) with Iron and Zinc maintenance dose.

3. Reduction of vitamin A –rich foods, or supplementation during infection , because of its ability to re-activate or increase susceptibility to respiratory viral infections; but vit A supplementation can be given after complete and certain resolution of covid 19 infection to stimulate alveolo-genesis.

4. Cathelicidin, to be given as inhaler or nebulizer to stop viral replication, mainly during the first 3 days of infection especially for patients who are unable to synthesize it .

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