Trop J Nat Prod Res, April 2023; 7(4):2675-2681 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

The Potential Role of Vitamin D Administration in The Skin Aging Process Through The Inflammatory Pathway: A Systematic Review

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ARTICLE INFO

Article history:
Received 06 July 2022
Revised 15 April 2023
Accepted 20 April 2023
Published online 01 May 2023

ABSTRACT

Skin aging occurs through various mechanisms, including the inflammatory process. Wrinkled and dry skin in the elderly is correlated with deficiency of vitamin D. Maintaining vitamin D at normal levels can suppress the degeneration process including skin aging. This study aimed to conduct a review regarding the effect of vitamin D administration on the skin, particularly on the inflammatory process. This review was conducted using the search engine namely Pubmed, Google Scholar, and Science Direct. The inclusion criteria included original articles, of both in vivo and in vitro studies, published in 2012-2022. A total of eight articles were obtained using the keywords namely inflammation, vitamin D, and aging. The findings demonstrate that vitamin D can reduce inflammation in the skin by reducing collagen breakdown, inhibiting high inflammatory response, and modulating activity immune response, as well as through its photoprotective effect. Vitamin D reduces collagen breakdown by decreasing MMP-1. Vitamin D suppresses inflammatory response by inhibiting the expression of inflammatory cytokines and decreasing the expression of growth factors. Vitamin D modulates activity related to immune response by increasing the percentage of Treg cells. Vitamin D has a photoprotective effect, which reduces thymine dimer by reducing nitric oxide and its products and increases the level of anti-inflammatory mediator. Inhibition of the expression of growth factors, proinflammatory cytokines, increased level of the anti-inflammatory mediator, following Vitamin D supplementation is associated with skin barrier repair. Thus, vitamin D regulates an anti-inflammatory pathway that may be exploited to slow the degradation process in skin aging.

***Keywords*:** inflammation, skin aging, vitamin D .

Introduction

Aging is a physiological process for humans. Based on United Nations' world population data in 2019, there were 703 million elderly people. It is estimated that the elderly population will increase by 1.5 times by 2050.[1] The increased number of elderly poses challenges in health problems,[2] as many molecular and cellular processes contribute to aging processes.[3] Accumulation of reactive oxygen species and imbalance of neutralizing products, in addition to molecular damage over time, dysfunction of mitochondria, and telomer shortening causing extrinsic and intrinsic aging process.[2,4]
The aging process occurs in all body systems, including the skin, which is the largest organ of the human body.[2]
The clinical manifestations of skin aging include thin and translucent skin, fine wrinkles, subduction of the cheeks and orbits, loss of underlying adipose tissue, lack of sweating, dry and itchy skin, hirsutism or hair loss, gray hair, and thinning of the nail plate skin.[4]

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Citation: Kristianti MTF, Goenawan H, Achadiyani A, Sylviana N, Lesmana RL. The Potential Role of Vitamin D Administration in The Skin Aging Process Through The Inflammatory Pathway: A Systematic Review. Trop J Nat Prod Res. 2023; 7(4)2675-2681 http://www.doi.org/10.26538/tjnpr/v7i4.1

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In addition, intrinsic aging is caused by accumulated damage of the cellular macromolecules resulting from the presence of free radicals and reactive oxygen species (ROS)[2], as the production of the latter increases during the aging process.[4]
The ROS in the skin is produced from the conversion of 1.5-5% of the oxygen consumed by the skin via intrinsic processes,[5] as the by-products of the electron transport chain of mitochondrial aerobic metabolism. The major sources of skin mitochondrial ROS are keratinocyte fibroblasts.[6] ROS play a role in molecular mechanisms in skin aging including those associated with oxidative stress and inflammation.[2] ROS also activates pro-inflammatory cytokines and also induces activation of TNF-α and TNF-β expression.[7] The presence of inflammation causes activation and infiltration of macrophages, which role is to remove oxidized lipids and damaged cells. Activated macrophages release matrix metalloproteinase (MMP) that degrades the extracellular matrix, causing degradation of the collagen matrix and formation of wrinkles in the skin.[8] Furthermore, macrophages release proinflammatory cytokines that aggravate the formation of wrinkles.[2]
UVB irradiation can induce IL-33 expression in normal epidermal keratinocytes and Tregs, which will then suppress other immune cells through IL-10 production, promoting skin aging. Tregs can be induced or accumulated depending on the regulation of inflammatory response associated with aging by the immune system.[9,10] T cells (Tregs) are involved in the negative regulation of the immune response by secreting IL-33 and IL-13 in response to tissue damage.[11]
Studies have reported an association between skin aging and vitamin D deficiency. The concentration of 7-dehydrocholesterol, a precursor of vitamin D3 in the skin, is reduced by 50% by the age of 80. In contrast, the total amount of pre-vitamin D3 in the young subject is twice as large as in elderly subjects.[12] A normal level of vitamin D3 is important to

prevent premature aging and maintain healthy skin aging.[13] Vitamin D3 in human keratinocyte cultures has been shown to stimulate the expression of genes involved in the anti-aging activity.[14] Furthermore, the active form of vitamin D, calcitriol, has many physiological functions,[15] which involve the role of Calcitriol and Vitamin D receptors (VDR) in regulating adaptive and innate immune responses, cell differentiation, detoxification of reactive oxygen species, apoptosis, angiogenesis, and invasion of various cell types.[16]

Vitamin D supplementation has been reported to help regulate the aging process.[17] Vitamin D has several beneficial effects, one of which is reducing inflammation through inhibition of inflammatory cytokine production, which is a salient characteristic of how the inflammatory response modifies cellular activity.[17,18] Vitamin D increases anti-inflammatory cytokines such as IL-10 and IL-4 and suppresses inflammatory cytokines such as IL-1, IL-2, TNF, and IFN-γ. Vitamin D3 also inhibits NF-kB, thereby partially suppressing IgE antibody class switches in B cells.[7,8] Aging has been reported to reduce pre-vitamin D production in the skin and changes the cytokine profile.[19] Therefore, restoring normal vitamin D levels may have an impact on reducing skin aging.[20] Thus, this study aims to review the effect of vitamin D on the inflammatory pathway of skin aging.

Method

Search strategy

Search engines Pubmed, Cochrane, Ebsco, and Google Scholar were used as data sources for searching articles on the effects of vitamin D in the skin aging process through the inflammatory pathway. Our review incorporates an intensive search of the literature through mistreatment of the keywords namely vitamin D, inflammation, aging, and other similar terms. International studies conducted between January 2012 and January 2022 were included in this review, whereas none of the duplicated studies were confirmed. The related analytical articles were compiled.

The first step in selecting articles and research was carried out by adjusting the criteria for the titles and abstracts of the gathered research. The inclusion criteria include articles of experimental studies, which were composed of both in vitro and in vivo studies published between 2012-2022. Other study designs, such as review articles, were not included in this review (Figure 1). The criteria are outlined in the Prisma diagram.

From each eligible study, the following data were retrieved: first author, year of publication, study group, intervention, and principal findings. The effect of vitamin D administration on inflammation associated with the skin aging process was described and compared. All data were analyzed and presented in Table 1.

Result and Discussion

A total of seven articles were used in this study, consisting of five articles of in vivo studies conducted on mice and humans, and two articles of in vitro studies conducted on skin cells. A summary of the findings from the review of articles related to the effect of vitamin D administration on the inflammatory process in the skin associated with aging is presented in Table 1.

The findings from a review of seven journal articles demonstrate that the administration of vitamin D reduces the levels of ROS and NO in skin cells, thereby reducing thymine dimers.[21,22] Vitamin D administration was reported to inhibit the expression of IL-1, IL-8, IL-22, TNF-, TGF-α, and VEGF, and reduce protein levels of MMP-1 and MMP-2.[25,26,27] Vitamin D administration has also been reported to increase the percentage of Treg cells in lymph nodes in dry skin and increase the anti-inflammatory mediator arginase-1 in the skin as well as the expression of genes associated with skin barrier repair.[23,24]

Skin aging is characterized by symptoms such as wrinkles, loss of elasticity, flabbiness, and rough and dry texture.[2] Dry skin occurs due to changes in the structure of the skin. In skin aging, the epidermal layer is thinner due to the shrinkage of keratinocytes, which results in increased water loss through the epidermis.[10] Another manifestation of skin aging wrinkles. A wrinkle is induced by the decreased collagen and elastin that provide tensile strength and elasticity.[4]

Another change in skin aging is a decrease in the production of sweat and fat which leads to thinning of adipose tissue.[10] In addition, the presence of oxidative stress also causes the oxidation of lipids, making them susceptible to inflammation.[28] This is because it is associated with a reduction in white fat tissue, which acts as an antibiotic barrier.[10] Fat cell depletion occurs because fibroblast cannot turn into adipose tissue.[10]

The action of Vitamin D to Reduce Collagen Breakdown

The study by Philips et al. reported that vitamin D significantly reduces MMP-1 and MMP-2 protein levels in melanoma cells,[26] which correlates to the mechanism of skin aging via the collagen breakdown pathway.

In the aging skin, the collagen breakdown increases due to increased expression of MMP, particularly MMP-1, resulting in a reduced level of total collagen. MMP-1, MMP-3, and MMP-9 are the MMPs that cause elastin breakdown, which reduces skin elasticity.[10] While MMP-1 is responsible for the breakdown of ECM,[29] overexpression of MMP-1 and MMP-3 may lead to collagen degradation, in addition to the role of MMP-9 in the final degradation of collagen fibrils following initial cleavage by collagenases such as MMP-1, MMP-8, and MMP-13.[8] The findings demonstrate the potential use of MMP as a primary marker for wrinkles caused by UVB through the inflammatory process in aging skin.[30]

Increased MMP levels are one of the skin aging processes that is associated with the inflammatory process.[2] Epidermal cells are subjected to oxidative stress due to UV radiation, which damages and oxidizes lipid cells, resulting in inflammation and eventual phagocytes to remove damaged cells and oxidized lipids.[2] In addition, activated phagocytes release MMPs to break down the extracellular matrix.[2] Repeated UV radiation damages the dermis epidermis junction by over-activating the complement system to release proinflammatory cytokines and ROS in the long term.[2] This means that natural aging and premature aging caused by UV evoke MMP expression.[31] The effect of vitamin D in reducing the amount of MMP-1 protein in the skin by neutralizing ROS in the MAPK pathway can further suppress MMP production and inhibit collagen degradation.[2] The presence of inhibition of MMP expression during vitamin D administration indicates that vitamin D has the potential for skin aging.

The action of Vitamin D Inhibit Inflammatory Response in Aging Skin

Philips et.al and Lopez et al have demonstrated that administration of vitamin D could inhibit the expression of IL-1, IL-8, IL-22, TNF-α, TGF-α, and VEGF.[25–27] These results are similar to those of Samanta et al., who reported that vitamin D can reduce the expression of IL-1, IL-6, IL-8, IL-13, and IL-22 and inhibit the expression of TGF-α, TGF-β, TNF-α, and VEGF.[32]

These results are consistent with previous studies showing that the active metabolite of vitamin D has an anti-inflammatory effect by inhibiting the expression and production of several anti-inflammatory cells, including IL-1β, IL-6, and IL-8.[33] Research Almerighi et al. also reported that vitamin D can inhibit the expression of anti-inflammatory cells such as IL-1, IL-6, IL-8, IL-12 and TNF-α.[34] The skin has a complex immune system. B and T lymphocytes, Langerhans cells, keratinocytes, and mast cells comprise the skin's immune system and various living molecules (chemokines, cytokines).[32,35]

Langerhans cells and mast cells are immune barriers and can be activated by neurotransmitters such as TNF-α, chemokines, and other NSAIDs produced by activated keratinocytes by activating activated T cells. This condition enhances the immune response in various ways.[35] Although keratinocytes are a major component of the epidermis that express receptors such as Toll 83 (TLR) and produce infectious inflammation and chemicals such as IL-1, IL-3, IL-6, IL-8, IL -33, TGF-α, TGF-β, and TNF-α.[36]

Meanwhile, skin aging can occur with an inflammatory process characterized by a high inflammatory response.[32] Aging fibroblasts have been shown to secrete several inflammatory agents such as IL-6, IL-8, and TNF-α.[10] Thus, by inhibiting the expression of IL-1, IL-6, IL-8, TGF-α, TGF-β, and TNF-α upon administration of vitamin D, then vitamin D has the potential as an anti-inflammatory agent. aging of the skin by reducing inflammation.

Table 1: Summary of effects of vitamin D administration on skin inflammation

Study design	Result	Inflammation effect	Reference
In vivo study Adult wistar rats (n = 32) each half female and half male Divided into 4 groups, apply of: PBS (n=8) Vit D3 100µg/ml (n=8) Vit D3 liposome (n=8) Aloe gel 1 ml (n=8) exposed by UVA dan UVB lamp 2 hours/day for 1 month	Color of female rat skin improved after treatment Vit D3 liposome (p<0,05) Colour of rat skin improved after treatment in Vit D3, VitD3 liposome, and aloe gel (p<0,01) Histological appearance of mouse skin with vitamin D3 slightly increased the production of new collagen fibers and skin integrity, but the dermis structure was loose Histological appearance of skin with vit D3. liposomes improve skin structure, the dermis and epidermis layers have clear boundaries, compact collagen fiber structure and an orderly arrangement of glands	Vit D3 reduces CPDs from UV sunburn, reduced level of ROS and NO in skin cell, decrease oxidative damage and DNA breakdown. Vit D3 repairs DNA via p53 protein expression.	Bi Ye *et al*. (2019)[21]
Clinical trial Human *ex vivo* skin (n = 3) Treatment of UV irradiated + 1 nM 1,25(OH)2D3 Treatment sham irradiated + 1 nM 1,25(OH)2D3 Analysed per time point 0.5; 1; 3; 6; and 24 hours	BP decreased after 1,25(OH)2D3 supplementation and UV irradiation on the skin ($p < 0.01$ at 0.5 h and $p<0.001$ at 3 h) TD level 68% after UV irradiation and 1,25(OH)2D3 supplementation in the skin at 24 hours ($p < 0.05$). The TD of the irradiated sham did not change significantly at any point in time	Vitamin D reduces thymine dimers by reducing NO and NO products	Song *et al.* (2013)[22]
In vivo study Female offspring BALB/c mice (n=12) Divided into 2 groups: Dietary vitamin D (2280 IU vitamin D/kg with 1% calcium) Not dietary vitamin D (IU vitamin D3/kg with 2% calcium) Observation for 336 hours	CD4+ TReg cell increased in the SDLN and reduced in the ADLN from mice with suplemengtation vitamin D to mice not suplementatin vitamin D, but there was no difference in the skin CD3+CD4+CD25+Foxp3+ cells in suplementation vitamin D > not suplementation vitamin D at SDLN and airway-draining lymph nodes (ADLN) (p< 0,05)	Vitamin D3 increases the percentage of Treg cells in the skin-drying lymph nodes (SDLN)	Gorman *et al.* (2016)[23]
Clinical trial Healthy adult (n=25) Divided into 4 categories: Plasebo 50,000 IU D_3 100,000 IU D_3 200,000 IU D_3	After 48 hours irradiation, expression of iNOS (p= 0.02) and TNF-α of skin in 200,000 IU D_3 < placebo (p = 0.04) Treatment significantly increases serum vitamin D3 levels (P = 0.007) Treatment increased arginase-1 (P = 0.005)	High doses of vitamin D3 supplementation increased serum vitamin D levels which significantly increased the anti-inflammatory mediator arginase-1 in the skin and the expression of genes associated with skin barrier repair.	Scott *et al.* (2017)[24]

Observation for 6 weeks UVR skin for 48 hours	Continuous treatment reduces reddened skin (P = 0.02)		
In vivo study Human neonatal dermal fibroblasts Divided into 3 categories: Non-irradiated UV-A radiated UV-B radiated Administration vitamin D at 0; 0.02; 0.2; or 2 µM Observation for 24 hours	Type I collagen protein levels in UVA irradiated and non-irradiated fibroblasts increased significantly after vitamin D supplementation at 0.2 and 2 M ($p < 0,05$) Elastin promoter activity in non-irradiated fibroblasts, UVA and UVB radiation was inhibited after vitamin D supplementation at 0.2 and 2 M ($p < 0.05$) Elastin promoter activity on UVA irradiated fibroblasts was inhibited after vitamin D supplementation at 0.02; 0.2 and 2 M ($p < 0.05$) Elastase activity in non-irradiated and UVA irradiated fibroblasts was inhibited after vitamin D supplementation at 0.2 M ($p < 0.05$) IL-1 protein levels were inhibited up to 64% and IL-8 protein levels were inhibited up to 63% in UVA-irradiated cells after vitamin D supplementation at 0.2 M ($p < 0.05$)	Vitamin D significantly inhibited the expression of IL-8 and IL-1 in UVA-irradiated fibroblasts	Philips *et al.* (2019)[25]
In vivo study Melanoma cells Divided into 5 categories based on vitamin D dosage: 0; 0.0002; 0.002; 0.02; 0.2 µM Divided into 2 group: control and 0.02 µM vitamin D Observation for 24 hours	All dosage vitamin D significantly inhibited membrane damage, IL-1,TNF-α, TGF-β, VEGF, MMP-2, and MMP 2, oxidative DNA/RNA damage, and stimulated superoxide dismutase protein levels ($p<0.05$) P53 promoter activity stimulated after administration with Vitamin D at 0.02, and 0.2 µM ($p < 0.05$)	Vitamin D significantly inhibits the expression of TNF-α, TGF-α, IL-1 and VEGF expression, and reduces the protein levels of MMP-1 and MMP-2	Philips *et al.* (2020)[26]
In vivo study Dendritic cells (DC) were differentiated from isolated human Monocytes Divided into 5 categories based on vitamin D dosage: 0; 0.01; 0.1; 1; 10 nM Observation for 48 hours	IL-22 expression and secretion inhibited after treatment ($p < 0,001$) IL-22 production in Th22 mono-cultures inhibited by vitamin D T cell activation is not affected by vitamin D	Vitamin D represses VDRE on the IL-22 promoter so that the production of IL-22	Lopez *et al.* (2021)[27]

Vitamin D Modulates Immune Response Activity

The review revealed that vitamin D3 increases the percentage of Treg cells in the skin-drying lymph nodes (SDLN),[23] such as that of Gorman et al., who reported that vitamin D increases the proportion of Treg cells in lymph nodes that burden the skin.[23] Regulatory cells namely FoxP3 CD4 + Tregs are crucial for maintaining the equilibrium of the immune system and tissues.[10] Tregs are linked to inflammatory pathways that cause skin aging. When skin ages, changes in skin structure and immunological composition, along with a reduction in Langerhans cells, cause antigen-specific immunity to deteriorate and the Foxp3 + Treg immune complex to rise.[10] Given that vitamin D has a direct impact on how keratinocytes in atopic skin diseases function internally, its impact on Tregs seems understandable. Additionally, the capacity of skin connective cells and Langerhans cells grow, leading Treg cells to produce FOXP3 and secrete IL-10.[35] In short, vitamin D suppresses the activity of T-cells to control the inflammation process.[37]

Most of the biological functions of vitamin D are mediated through the regulation of gene expression.[38] Active vitamin D3 binds to its nuclear receptor (nVDR) with high affinity and specificity.[39] Vitamin D3-nVDR forms heterodimers with retinoid X receptors, which then enhance or suppress transcription of target genes by binding to the active component of vitamin D in DNA.[33,39] nVDR is found in various immune system components such as human Treg cells, dendritic cells, B cells, T cells, Lagergens cells, and phagocytes.[33] Vitamin D3-VDR complex also modulates innate immunity by regulating the development and activation of NKT and NK cells, as well as the production of IL-4 and IFN-γ.[40] Vitamin D can inhibit the transcriptional activity of NF-kB. In addition, Vitamin D indirectly inhibits ROS by suppressing the activity of NF-kB,[33,41] suggesting the potential use of vitamin D as an anti-aging agent that can suppress T cell activity to control the inflammatory process.

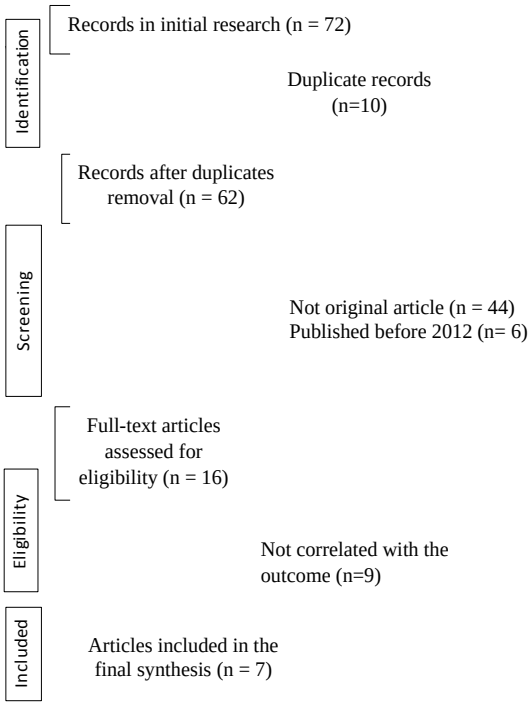

Figure 1: PRISMA Diagram

Photoprotective Effect of Vitamin D

The findings also suggest that vitamin D reduces thymine dimer by reducing nitric oxide (NO) and NO products. The formation of thymine dimers is recognized as one of the symptoms of DNA damage caused by UV exposure.[42] Increased UV regulation of NO synthase and the release of NO from the breakdown of endogenous NO reserves by UVA radiation causes an increase in the synthesis of nitric oxide (NO).[22] UV light also encourages peroxidation ROS, which causes inducible nitric oxide synthase (iNOS) to be expressed in aging skin. iNOS activates endothelial growth factor (VEGF) to promote angiogenesis and permeability of the cell.[7] Song et al. claimed that vitamin D3 lowers nitrotyrosine levels and functions as a photoprotective agent to prevent DNA damage in the skin to preserve the skin barrier. Thus, the reduction of reactive nitrogen species is necessary for the prevention of aging.[22] Song et al. also reported that supplementing with high doses of vitamin D3 can raise serum vitamin D levels, which in turn can significantly boost production of the anti-inflammatory mediator, arginase-1, and the expression of genes related to skin barrier repair.[24] Additionally, arginase dysregulation affects death signaling pathways directly in aging processes, or indirectly via hampered NO pathways, metabolic, and mitochondrial malfunction, or elevated oxidative stress.[43]

However, one paper was found in the review's findings that claimed vitamin D levels are unrelated to skin photodamage,[44] which contradicted the evidence presented by Gordon et al. concerning the photoprotective effect of vitamin D. Additionally, studies have shown that Vitamin D can inhibit UV radiation-mediated DNA damage and induce of cellular skin defenses.[45] Research by Bi Ye et al. revealed that vitamin D supplementation decreases ROS and NO produces from UV sunburn, preventing DNA damage in the aging process[21]. By reducing the level of proinflammatory factors associated with UV radiation, vitamin D works as a photoprotective, preventing membrane cell damage and boosting cell viability.

Skin aging is mediated by an inflammatory process stimulated by oxidative stress, which increases inflammatory factors produced by immune cells, including PTGS2, iNOS, and cytokines, as well as IL-6, IL-1β, and TNF-α. This component causes skin integrity to deteriorate and collagen fragmentation to rise, causing the skin to age.[46] According to this review, vitamin D supplementation can reduce the levels of TNF-, TGF-, IL-1, IL-3, and IL-8 in the body. The formation of MMP can be halted by inhibiting these inflammatory cytokines, which helps to stop the deterioration of skin integrity that leads to skin aging. Figure 2 summarizes how vitamin D treatment affects the inflammatory process to preserve the integrity and prevent skin barrier damage.

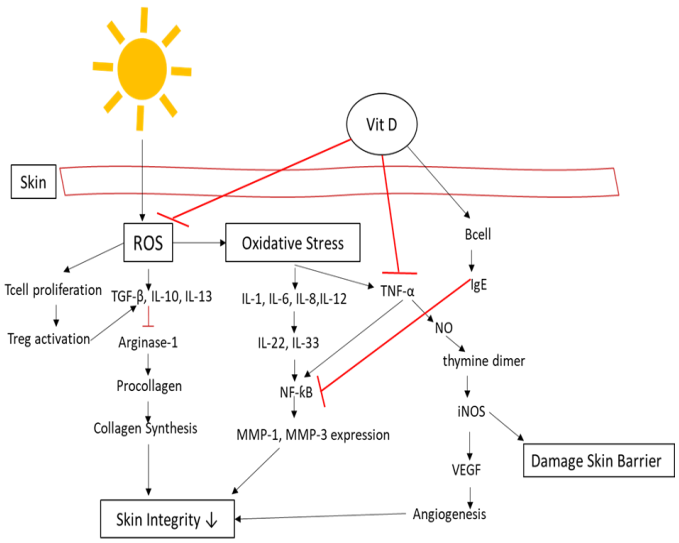

Figure 2: Vitamin D prevents ROS and its numerous mechanisms. Vitamin D reduces the inflammatory cell cycle of the skin, Treg activation, TGF-β, TNF-α, and NF-ƙB to maintain skin integrity and prevent damage to the skin barrier.

Conclusion

Vitamin D administration could reduce inflammatory responses, reducing collagen breakdown, modulating immune response activity, and having a photoprotective effect in skin. The modulation of inflammation pathway were induce by the production of Treg cells, which causes a decrease in proinflammatory cytokines such as IL-1, IL-6, IL-8, IL-22 and reduced expression of TGF-α, TGF-β, TNF-α, and

VEGF, as well as that of MMP-1. Vitamin D also decreases the levels of NO and thymine dimers and increases the level of arginase 1. Additionally, decreased expression of proinflammatory cytokines and growth factors as a result of suppressed ROS may decrease MMP-1 expression, potentially through inhibition of protein-1 (AP-1) and/or NF-B activation, which hampers collagen and elastin degradation in the skin, resulting in delayed skin aging. Thus, it suggests that Vitamin D has potential role to slow down the aging process since it blocks pathways relevant to the mechanism of skin aging. However, most of studies in this review were done in culture or model skin aging. Further research is needed to focus on the impact of vitamin D on actual aged skin and how it functions as an anti-aging agent.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

This project was supported by grant funding for NS from Universitas Padjadjaran (Riset Percepatan Lektor Kepala), grant number: 1959/UN6.3.1/PT.00/2021.

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