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Review Article

Light Emitting Diodes as a Phototherapy Light Source for Increasing Vitamin D: A Review

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ABSTRACT

Phototherapy is treatment that uses UV light. However, other light variations can be used for phototherapy. One of them is a light-emitting diode (LED), which is known to be more efficient than other light sources. This review aims to discuss the effectiveness of light-emitting diodes (LED) as a phototherapy light source for increasing Vitamin D. Studies from online databases (Pubmed, Proquest, and Science Direct) published around 2012 to 2022 were included in the review. A combination of search strings i.e., ("LED" or "Light Emitting Diodes") AND ("VITAMIN D3" or "VITD3" or "25(OH)D") were used in the literature search. Twelve research articles (human- or animal-based) showed that LED UV exposure increases vitamin D. Several articles showed that LED UV is more effective and efficient in producing vitamin D compared to natural light. This review showed that LEDs are a potential light source for phototherapy to increase vitamin D, even better compared to sunlight, and using LED as a therapeutic device is a novel technique in medical treatment and can reduce related medical costs.

***Keywords*:** Light emitting diodes, phototherapy, vitamin D, human and health, medical treatment

Introduction

Since ancient times, light treatment has been known as phototherapy using ultraviolet radiation with specific wavelengths for therapeutic purposes. Ultraviolet (UV) are electromagnetic rays with a wavelength shorter than visible light and consist of ultraviolet A (UVA) (400–320 nm), ultraviolet B (UVB) (320–280 nm), and ultraviolet C (UVC) (280–200 nm).[1] Heliotherapy, often known as solar therapy, has been used for many years to cure skin conditions. Three thousand five hundred years ago, some countries like Egypt and India developed skin treatments with seeds or plant extracts and exposure to sunlight.[2]

Phototherapy is a treatment that uses UV light, and it can be done with exposure to natural light, UVA, or UVB. The wavelengths and UV dose will be regulated depending on the proposed indication.[2] Ultraviolet radiation is absorbed through the chromophores. Chromophores are molecules that are capable of absorbing specific wavelengths such as nucleotides, DNA, melanin, lipids, amino acids, trans-urocanic acid,[2] tattoo pigments, porphyrins, photosensitizing drugs, and 7- dehydrocholesterol (7-DHC, provitamin D3).[3] Ultraviolet radiation can modify the structure and function of the chromophores. These modified molecules are termed photoproducts, and they are involved in photocarcinogenesis, inflammation, apoptosis, and immunosuppression.[2] The absorption of radiation by chromophores leads to photochemical reactions and possible immune reactions.[4]

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Modern research on human physiological and pathological changes has revealed that UVR can have both advantageous and detrimental effects.[5] In general, ultraviolet rays are considered unsafe for the human body. However, it benefits the body in terms of vitamin D production, a factor necessary for human health, which is beneficial by reducing some diseases. Vitamin D is obtained in minimal amounts from the diet and primarily generated in the body after exposure to UVB rays from the sun to the skin. Therefore, current research suggests getting enough UVB exposure for enough vitamin D production.[6]

Ultraviolet radiation leads to numerous skin diseases: irregular pigmentation, photoaging, sunburn, and skin cancer. UVR triggers the formation of reactive oxygen species (ROS), causing disruption of cell structures and oxidative stress accumulation in cells causing photoaging.[1] On the contrary, UV light has well-known beneficial purposes, as well as its therapeutic functions in jaundiced infant treatment, skin medication, control of emotion, sleep, seasonal affective disorders, wound healing, vitamin D deficiency, and other medical applications.[7]

The significant valuable effect of UVR is the synthesis of vitamin D in the cutaneous when UVB is absorbed by epidermal 7-DHC.[8] UVR exposure promotes vitamin D production that can modulate innate and adaptive immune responses.[9] Ultraviolet B radiation changes the skin's 7-DHC (provitamin D3) to pre-vitamin D3 (previtD3), which is unstable and needs warmer temperatures to convert to vitD3. Within farther irradiation, previtD3 is converted into lumisterol and tachysterol.[10]

Vitamin D is known as a prohormone and a fat-soluble vitamin. Vitamin D is also crucial for phosphate and calcium balance affecting bone health; otherwise, its insufficient content will result in osteomalacia and rickets. However, novel data support that vitamin D serves purposes other than bone metabolism.[11, 12] Vitamin D is associated with cardiovascular disease, osteoporosis, diabetes, multiple sclerosis, chronic pain, respiratory infection, cancer,[13] and kidney disease.[14] 1,25-dihydroxyvitamin D is a steroid hormone that controls genes in more than 30 distinct organs, such as the liver, the

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brain, kidneys, and prostate, as well as Ca metabolism and bone health. It also plays a significant role in controlling cell proliferation, modulation of immune systems, and cardiovascular health.[15]

Given that the daily, monthly, and latitude variations in UVB intensity depend on changes in the thickness of the ozone layer, aerosols, air pollution and clouds, and individual susceptibility, it is nearly impossible to provide recommendations for the appropriate duration of sun exposure.[15] However, due to aging, use of sunscreen, latitude and season, and indoor-focused lifestyles in modern civilization, many people receive deficient sun UVB exposure, resulting in an inadequate vitamin D nutritional status globally.[16] It is advised to keep the level of serum 25(OH)D at a minimal 30 ng/mL (75 nmol/L) and preferably at 40-60 ng/mL (100-150 nmol/L) by seeking enough sunlight irradiation or from vitamin D intake for health benefits. However, the ideal level of serum 25-hydroxyvitamin D is still arguable.[17]

As a result, the UVB dose needed cannot be fully satisfied by natural light. Devices that artificially produce acceptable UVB dosages have been offered as a solution to this problem. However, the use of these UVB irradiation devices is restricted by the need to expose specific body areas to certain lights at specific distances and the fact that the devices are used only for a few specific types of therapies. Research on the creation of general illumination that emits UVB to people who are not frequently exposed to natural light is lacking.[12] A variety of equipment, such as lasers, halogen lamps, arc/flash lamps, fluorescent lights, and light-emitting diodes (LEDs), provide visible light as a therapeutic modality[18]. Several studies using UVB tube lamps were shown to increase the vitamin D serum in animals [10, 19, 20] As well as in vitro studies have shown that the specific UV narrow band of 295 nm was shown to efficiently increase the production of previtamin D3 in ampoules and vitamin D3 in human skin in a dose-dependent manner.[21]

Artificial lighting is the main source of electricity globally. Over the next 40 years, lighting services, particularly in developing nations, warrant further development. LED as economical light-source technology can cut down the energy and environmental impacts of these services.[22] Light sources using LED with various optical UV and IR characteristics as well as the visible light characteristics of natural light have recently been produced. Although LEDs have a high manufacturing cost, they are a low-power and high-efficiency light source. Its capacity also deals with a variety of optical features which can be replicated for use in industrial applications.[12]

Materials and Methods

Studies included in the review were selected from online databases (Pubmed, Proquest, and Science Direct). They were articles published from 2012 to 2022. Search terms used were a combination ("LED" or "light emitting diodes") AND ("VITAMIN D3" or "VITD3" or "25(OH)D"). The selected articles were full-text articles written in English, addressed human or animal studies, and used observational designs, which include a control and/or comparison group (e.g., case-control, cohort, or longitudinal study) and accepted methods to assessing UV wavelength and light source. Articles outside of these inclusion criteria were eliminated from the list. In reviewing the articles, the reviewers determined a research question "What are the advantages of LEDs when compared to other light sources? And does UV LED significantly increase vitamin D?"

Results and Discussion

After the literature search from databases using the determined keywords, duplicated articles in more than one database were removed. After duplication checks and matching with inclusion and exclusion criteria, 12 articles were finally selected. Those articles consist of 2 human studies, 1 in vitro study, and 9 animal studies, which broadly showed that UV LED can increase vitamin D levels (Table 1).

The result of this review found that LEDs are a potential light source for phototherapy to increase vitamin D. However, it seems very challenging to compare the exposures used in each study because different devices used might result in different effectiveness which is also influenced by some other factors, such as the wavelength (nm), irradiance (W/cm2), dose (J/cm2), exposure time (s), number of exposures, cell type, recovery period, or subject characteristics.[34]

Most of the human or animal studies showed that UV LEDs increase serum vitamin D levels,[15, 23-29, 31, 32] although one article showed a decrease in vitamin D levels after exposure to UVB LEDs in the first intervention and then increased in the second intervention.[33] One article showed no significant difference in the levels of calcium, phosphor, 25(OH)D3, or 1,25(OH)2D3, after the irradiation time, but 7-DHC levels were significantly influenced by UVB-LED exposure.[30] The 25(OH)D level in the blood of rats exposed to UVB LED illumination was higher than that under general illumination.[29]

The wavelength is very important in phototherapy because the biological components of the skin have several important absorption ranges at certain wavelengths. Some of the most common tissue components are water, blood, proteins, lipids, and other chromophores that have spectra between 200 and 1200 nm.[35] The result of ultraviolet light on target cells and tissues is triggered by molecular and cellular pathways which are induced when UV light is absorbed by chromophores in the skin, and each chromophore can only absorb certain wavelengths.[2] One of the chromophores is 7-dehydrocholesterol (provitamin D), and a certain wavelength is needed to activate it. Kalajian et al.[25] found that 293 nm LED was the most suitable for human trials due to more than 50% shorter irradiation time to produce the same amount of vitamin D3 as other LEDs, but other studies found different wavelengths are also effective in increasing vitamin D3. Hence, it can be said that UV light with a wavelength between 268 and 316 nm can activate the production of vitamin D in the body.

Many different doses are used for UV exposure. Perhaps, such doses affect the level of vitamin D in the blood. The amount of dose depends on the irradiance, distance of the UV source to the object, and the duration of exposure. Longer exposure to UV will increase the dose of light received by the object. Determination of the wavelength and dose of radiation energy varies depending on the treatment indications. UVB therapy can be applied 3 to 6 times a week. Many studies use 2 to 3 times a week.[2] When compared to administering 20 or 40 g of vitamin D orally every day, exposure to narrowband UVB given three times a week boosted levels of 25(OH)D more.[33]

The quantity of vitamin D produced also depends on how long the treatment lasts. This Duration of treatment determines toxicity prevention when the body cannot produce too much vitamin D. A negative feedback system ensures that vitamin D production as a result of exposure to UVB light never reaches dangerous levels. Previtamin D will transform into lumisterol and tachysterol if exposed to UVB for an extended time.[34]

Daily UVB-LED irradiation can elevate serum 25(OH)D levels although that is not always the case. Even though this shows a true biological change, some factors perhaps contribute to this abnormality. 25(OH)D may show as a negative feedback loop for 25-hydroxylase in the liver and cause hydroxylation of vitD3 to 25(OH)D. Turning 25(OH)D to 1,25(OH)2D metabolite may represent part of the reduced 25(OH)D. The decline may be due to people spending more time indoors, thus, reducing the production of 25(OH)D. The other factor is the season that affects sinusoidal changes in 25(OH)D concentrations.[33]

Besides being influenced by external factors, the production of vitamin D in the body is also strongly influenced by VDR polymorphism. The other factor that is most biologically active from vitD is 1,25(OH)2D3, which attaches to the vitamin D receptor (VDR). The biological activity of 1, 25(OH)2D3 is carried out via VDR, a nuclear receptor.[36] The vitamin D receptor is a part of the steroid receptor family of transcription factors.[37, 38] Started with ligand binding, the VDR interacts with the retinoid X receptor (RXR) to form a heterodimer, which then attaches to vitamin D response elements (VDREs) in target genes to promote the expression of those genes. 1,25(OH)2D3 has been predicted to regulate over 200 genes and affect a heterogeneity of cellular processes.[39]

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Table 1: Summary of the literature review on related available research articles for UV LED as a phototherapy light source for increasing vitamin D

No	Author	Article's title	Sample	Light source	UV wavelength	Finding
1	Morita et al.[23]	Short-range Ultraviolet Irradiation with LED Device Effectively Increases Serum Levels of 25(OH)D	Mice (serum)	UV LED	268, 282, 290, 305, 316 nm	Narrow-range wavelengths ultraviolet irradiation provided by a UV-LED lamp is effective in increasing vitamin D levels at 316 nm, previously considered to be an ineffective wavelength for previtamin D3 production.
2	Barnkob et al.[24]	Investigation of the Effect of UV-LED Exposure Conditions on the Production of Vitamin D in Pig Skin	Pig (skin)	UV LED	280-340 nm	Vitamin D3 in pig skin was produced after the pig skin was irradiated with LED-UV with optimal wavelength 296 nm. The maximum dose of 20 kJ/m2 produced vitamin D3 3.5–4 μg/cm2.
3	Kalajian et al.[25]	Ultraviolet B Light Emitting Diodes (LEDs) Are More Efficient and Effective in Producing Vitamin D3 in Human Skin Compared to Natural Sunlight	In vitro: Human skin	UV LED	293, 295, 298, 305 nm	293 nm LED was the most suitable for human trials due to more than 50% shorter exposure time to produce the same amount of vitamin D3 as other LEDs and was also found to be 2.4 and 2.5 times more efficient in producing vitD3 in Type II and III of human skin, respectively, compared to exposure to the same amount of solar energy in a much shorter time.
4	Cusack et al.[26]	Effects Of A Light-Emitting Diode On The Production Of Cholecalciferol And Associated Blood Parameters In The Bearded Dragon (*Pogona vitticeps*)	Bearded dragon (serum)	Standard fluorescent bulb (UVB), non-UVB bulb, LED UVB bulb	10% UVB (280-320 nm) and 30% UVA (320-400 nm)	The plasma concentration for 25(OH)D3 in the LED group was greater than that of UVB (p = 0.0347) and the UVBN (p = 0.0490) groups.
5	Guo et al.[27]	The Effects of Ultraviolet Supplementation to the Artificial Lighting on Rats' Bone Metabolism, Bone Mineral Density, and Skin	Rat (serum, bone, skin)	UV LED	280-340 nm, peak at 315 nm	Phase 1, there was no significant change and significant difference (p > 0.05) in the concentrations of 25(OH)D between two groups. At the end of phase 2, there was a significant increase in 25(OH)D level in both groups. Although the concentration of 25(OH)D was less in the UV group than in the control group, there was still no significant difference (p > 0.05). UV irradiation does not significantly affect the concentration of 25(OH)D when vitamin D is present in sufficient amounts.
6	Morita et al.[28]	Effects of Ultraviolet Irradiation with a LED device on Bone Metabolism Associated with Vitamin D Deficiency in Senescence-accelerated Mouse P6☆	Mice (serum)	UV LED	305 nm	UVR increased 25(OH)D and 1,25(OH)2D levels after four and eight weeks of UVR in the D-UVR+ group compared to that in the D-group (p < 0.05). The relative micro–CT trabecular bone mineral density values were higher in the D-UVR+ group than in the D-group at 8 weeks UVR (p = 0.048). Peak load

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						was significantly higher in the D-UVR+ group than in the D- group (p = 0.036). Significantly fewer osteoclasts and less immature bone could be observed in the D-UVR+ group than in the D-group in the histological assay.
7	Oh & Lim.[29]	Development and Effect Analysis of UVB-LED General Lighting to Support Vitamin D Synthesis	Rat (serum)	UVB-LED General Lighting or Normal Lighting	280-315 nm	Analytical results showed that the measure of 25-hydroxyvitamin D [25(OH)D] in the blood of rats exposed to UVB LED illumination on the 7th and 14th day, respectively, was higher than that under general illumination. Vitamin D synthesis in the human body can be supported by lighting.
8	Wei et al.[30]	Effects of B-Wave Ultraviolet Supplementation Using Light-Emitting Diodes on Caged Laying Hens during the Later Phase of the Laying Cycle	Hen (serum)	UVB LED	296–316 nm	There was no significant difference in the levels of Ca, P, 1,25(OH)2D3 or 25(OH)D3 over the exposure time (0, 4 and 8 weeks) in any group. 7-DHC levels were significantly influenced by UVB-LED exposure ($p < 0.01$). Furthermore, P content and 1,25(OH)2D3 concentration were significantly influenced by exposure duration but not by UVB-LED exposure ($p < 0.05$).
9	Ochiai et al.[31]	Short‐range UV‐LED Irradiation in Postmenopausal Osteoporosis Using Ovariectomized Mice	Mice (serum, bone)	UV LED	316 nm	UV radiation with a short-range LED device increased serum vitamin D levels and leads to an increase in BMD and bone strength.
10	Lin et al.[32]	Low Dose Ultraviolet B Irradiation at 308 nm with Light‐Emitting Diode Device Effectively Increases Serum Levels of 25(OH)D	Mice (serum)	UV LED	308 nm	Narrow-band LED UVB 308nm is effective in normalizing serum vitD in severe VDD at a dose not exceeding 355mJ/cm2 within three weeks.
11	Lee et al.[16]	The Effect of Proto-Type Wearable Light-Emitting Devices on Serum 25-Hydroxyvitamin D Levels in Healthy Adults: A 4-Week Randomized Controlled Trial	Human (serum)	UVB LED	285 nm	A significant difference in changes in serum 25(OH)D levels from baseline was observed between the experimental and control groups after two (0.25-3.10 ng/mL vs. 1.07-2.68 ng/mL, p = 0.009) and four weeks intervention (0.75–3.98 ng/mL vs. 1.75–3.04 ng/mL, p < 0.001). The mean total production of 25(OH)D after UVB exposure was predicted at 0.031 ng/ml per 1 cm2 skin area
12	Lee & Joo.[33]	Effects of Narrowband Ultraviolet B Exposure on Serum 25-Hydroxyvitamin D Concentrations: A pilot study	Human (serum)	UVB LED	nm	Serum 25(OH)D levels were reduced in both subjects at the end of the 1st intervention (32.1-21.4 ng/mL and 33.9-21.4 ng/mL, respectively), while serum 25 (OH)D levels increased during the two weeks of treatment were the second intervention (29.5 and 28.0

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ng/ml, respectively). At the end of the second intervention, the 25(OH)D concentrations were 19.0 and 20.4 ng/ml, respectively.

The role of the different VDR polymorphisms can be interpreted as such that each effect alters according to key factors such as genes and cell types.[40] VDR polymorphism has been linked to an elevated risk of some diseases with several genetic variants being less reactive than others to 1,25(OH)2D3 in suppressing inflammatory processes.[38]

The modernized purpose of light in medication was initiated in the 19th century with fast enhancement in understanding both the physical properties of light and basic interactions between light and matter. A marked example of an early triumph of phototherapy is the ultraviolet-triggered remedy of lupus vulgaris developed by medical doctor Niels Finsen.[41] Remarkable advances have been made in the scope of light-emitting diodes (LEDs) in the last few decades and have previously been accepted in biomedical research. Further, UV LEDs have significantly evolved. The developed UV LEDs include ultraviolet A, ultraviolet B, and ultraviolet C LEDs with emission peaks ranging down to 210 nm. LEDs have already outperformed all other lighting technologies in terms of conversion efficiency, making them a potentially optimal substitute for current solutions.[7]

Measurement of exposure intensity is crucial for reducing or avoiding potential side effects like burning, itching, and even cancer. To determine every person's daily UV exposure, Park et al. created a UVB LED lighting system based on an ultraviolet dose computation algorithm.[6] While LED lighting technologies that may supply UVB radiation are currently under research, a portable UV meter has been created to educate consumers about the UV strength of outdoor sunshine.[6] The use of UVB rays as therapy must be meticulous by considering the wavelength, dose, duration of exposure, and duration of treatment to avoid the side effects.

Conclusion

LEDs are a potential light source for phototherapy to increase vitamin D, even better than sunlight. Besides that, LEDs also have other advantages. They result in lower energy consumption, longer expected lifespan, lower maintenance costs, and reduced environmental impacts. UV LEDs of different wavelengths can be developed and used more widely as light sources in phototherapy. The use of LED as a therapeutic device is a novel technique in medical treatment and can reduce related medical costs. Therefore, this literature review suggests that UV LEDs can be further developed for medical purposes.

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.

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