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Sunlight-Induced Bioactive Mediators and Systemic Physiological Effects Beyond Vitamin D

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Abstract

Background: Solar radiation regulates human physiology through photochemical, vascular, immunological, neuroendocrine and retinal mechanisms. The extent to which these responses translate into clinically meaningful benefit varies greatly. Beyond its traditionally recognized role in vitamin D synthesis, sunlight activates multiple biological pathways involving nitric oxide-related species, neuropeptides, immunoregulatory mediators, and retinal photoreception.

Objective: To critically examine the bioactive mediators, molecular pathways, physiological responses, and potential clinical benefits of sunlight exposure beyond vitamin D, integrating evidence across cardiovascular, immunological, neuroendocrine, neurological, metabolic, and dermatological systems.

Methods: A structured, non-systematic literature review was informed by targeted searches of publicly accessible PubMed-indexed records and relevant reviews through November 2026. Primary human and experimental studies, systematic reviews and clinical trials were prioritized. Searches of subscription databases and gray-literature repositories were not completed; no claim of exhaustive retrieval is made.

Synthesis: Human UVA experiments demonstrate transient vasodilation and blood-pressure changes consistent with mobilization of cutaneous nitric oxide species. UV exposure also induces epidermal neuropeptide and immune pathways, including beta-endorphin, melanocortins and immunoregulatory mediators; systemic clinical implications remain incompletely established. Daylight reaching the retina provides robust circadian timing signals. Experimental metabolic findings have not been validated as preventive interventions in humans. Observational associations with cardiovascular and overall mortality are heterogeneous and vulnerable to confounding.

Conclusions: Beyond vitamin D, the most firmly established systemic effects of light involve circadian regulation and acute UVA-associated vascular responses, whereas several additional molecular pathways remain promising but incompletely translated into clinical benefits. Sunlight engages several biologically important pathways, but a molecular response is not synonymous with a net health benefit. Clinical translation should distinguish daylight exposure from ultraviolet exposure and prioritize rigorously assessed outcomes and photoprotection.

Keywords: sunlight, ultraviolet radiation, nitric oxide, photobiology, beta-endorphin, melanopsin, immunoregulation, circadian rhythm, cardiovascular physiology

1. Introduction

Sunlight has well-established roles in synchronizing human circadian timing, supporting daytime alertness and regulating sleep–wake behavior. Experimental work also identifies rapid vascular signaling and diverse skin-derived photochemical and immunological responses. Yet these effects are often grouped under the imprecise label “benefits of sunlight,” obscuring important differences between visible light, UVA, UVB and infrared radiation. A mechanistic response may be adaptive, neutral or harmful depending on intensity, duration, host susceptibility and clinical context [1–3].

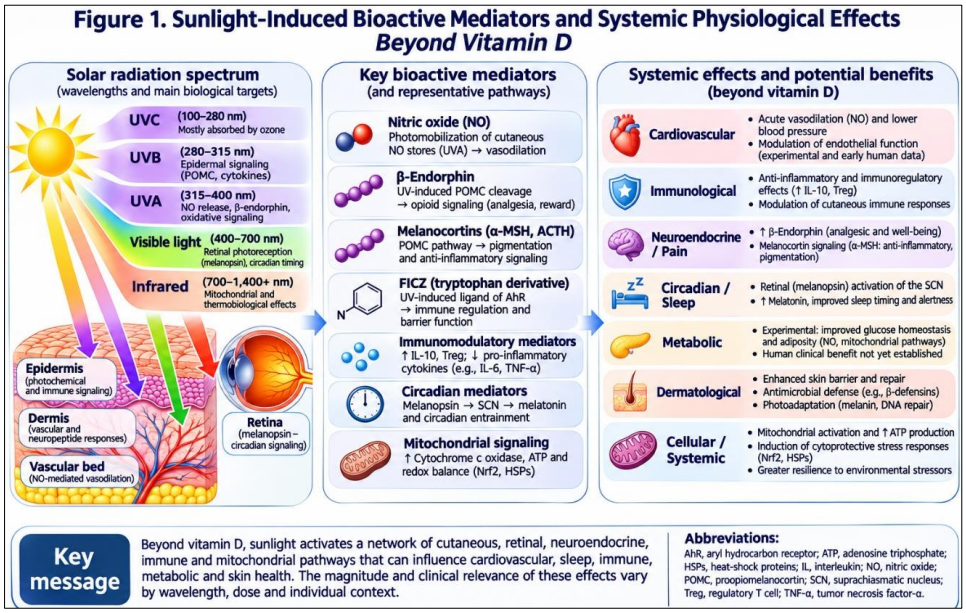


Fig 1: Sunlight-induced bioactive mediators and their systemic physiological effects.

This comprehensive narrative review focuses specifically on the biological effects of sunlight beyond vitamin D, identifying the principal photoinduced bioactive mediators, their molecular mechanisms, and their potential physiological and clinical benefits across human organ systems**.** In particular, observational associations cannot be interpreted as proof of protection because outdoor activity, ambient temperature, season, occupation and socioeconomic factors covary with exposure [3]. The principal physiological effects and potential clinical benefits of sunlight exposure, together with their underlying mechanisms, level of evidence, and limitations, are summarized in Table 1.

Table 1: Clinically relevant effects of sunlight and daylight: benefit, mechanism, and evidentiary boundaries

Outcome / potential benefit	Relevant exposure and mediator	What has been observed	Clinical interpretation and limitations	Refs
Circadian entrainment and daytime alertness	Visible daylight → retinal melanopsin/ipRGC → suprachiasmatic clock	Retinal light sensing establishes a mechanistic route for circadian phase regulation; human observational studies link daily light exposure to sleep–wake measures.	Established biological role of light; benefit does not require cutaneous UV exposure. Timing, intensity and prior light history matter.	2,5,6,15
Transient reduction in arterial blood pressure	UVA → cutaneous nitrite/nitrosothiol photochemistry → NO-related vasodilation	Controlled human irradiation experiments documented acute vasodilation and lower blood pressure.	Acute physiological benefit is plausible; sustained hypertension control or fewer cardiovascular events are unproven.	7–10
Improvement in inflammatory skin disease under treatment	Prescribed narrowband UVB → local immune and keratinocyte effects	Randomized clinical evidence supports narrowband UVB phototherapy in psoriasis.	Therapeutic benefit concerns medically dosed phototherapy, not unsupervised sun exposure.	17
Possible neurobehavioral / nociceptive modulation	UV → cutaneous POMC/β-endorphin signaling	UV-induced β-endorphin responses shown in mouse models and human skin.	Systemic analgesia, mood improvement or addiction-like effects in humans are not established as clinical benefits.	12,13,20
Potential metabolic regulation	UV exposure → NO-related and immune/metabolic pathways	Reduced obesity-related metabolic abnormalities in experimental mice.	Not a demonstrated human preventive or therapeutic benefit.	16
Potential systemic immune regulation	UV → cis-urocanate, cytokines, antigen-presenting cells, regulatory pathways	Mechanistic literature demonstrates local and potentially systemic immunomodulation.	Immune suppression is not inherently beneficial; UV can aggravate lupus and increase skin-cancer risk.	14,20,21
Associations with cardiovascular and overall mortality	Ambient sunlight / UV (multiple correlated exposures)	Epidemiological reviews report mixed associations with mortality and cardiovascular outcomes.	Causality is uncertain; outdoor activity, climate and socioeconomic confounding limit interpretation.	3,9,24

Notes: "Benefit" is reserved for clinically useful outcomes or well-established physiological functions; molecular responses and associations are identified separately. Evidence labels are narrative judgments, not formal GRADE assessments.

Abbreviations: ipRGC, intrinsically photosensitive retinal ganglion cell; NO, nitric oxide; POMC, proopiomelanocortin; UV, ultraviolet; UVA, ultraviolet A; UVB, ultraviolet B.

2. Scope and Literature Approach

This critical narrative review focused on sunlight-induced bioactive mediators and systemic physiological effects beyond vitamin D. Targeted searches of accessible PubMed-indexed records, publisher sources, and reference lists were conducted using combinations of terms related to solar radiation, ultraviolet and visible light, infrared radiation, nitric oxide, neuropeptides, melanopsin, circadian regulation, immunomodulation, metabolic pathways, cardiovascular physiology, and clinical outcomes. Landmark experimental studies, human physiological investigations, clinical trials, and relevant reviews were selected according to mechanistic relevance and clinical interpretability. The review was informed by SANRA principles [4]. Comprehensive searches of Embase, Scopus, Web of Science, LILACS, and gray-literature databases were not completed; consequently, this work does not claim exhaustive literature retrieval or constitute a systematic review.

3. Spectral Specificity and Biological Targets

Solar radiation is a mixture of ultraviolet, visible and infrared wavelengths. UVA penetrates deeper into skin than UVB and can mobilize photolabile nitrogen oxide-related species. UVB strongly engages epidermal DNA-damage responses and keratinocyte signaling. Visible light is sensed by retinal rods, cones and intrinsically photosensitive retinal ganglion cells (ipRGCs), which project to the suprachiasmatic nucleus and other neural targets [5, 6]. The biological route therefore determines the intervention: outdoor daylight can support circadian entrainment without deliberately exposing skin to UV. Figure 1 provides an integrated overview of the principal spectral components of sunlight, their associated bioactive mediators, and the resulting cardiovascular, immunological, neuroendocrine, neurological, metabolic, and cutaneous responses. The figure distinguishes established physiological effects from emerging mechanisms whose clinical benefits remain uncertain.

This distinction is crucial for causal inference. A reduction in blood pressure after a controlled UVA exposure cannot be generalized to daily outdoor sunlight; likewise, light-mediated improvement in circadian phase does not imply a need for UV radiation. Different endpoints require separate dosimetry and mechanistic attribution.

3.1. Photons, Chromophores, and Biological Dose

The biological response to solar radiation depends on wavelength, photon flux, exposure geometry, tissue optics, and the identity of the absorbing chromophore. An observed effect of full-spectrum daylight cannot be assigned to UVB, UVA, or visible light without wavelength-resolved experiments. This distinction is especially consequential when interpreting field studies in which heat, exercise, ambient air pollution, and behavioral changes occur simultaneously. Photochemical activation of cutaneous stores and retinal signaling represent fundamentally different exposure pathways, with distinct opportunities for intervention and different safety profiles [1, 5, 6].

3.2. Skin as an Endocrine and Immunological Interface

The epidermis contains keratinocytes, melanocytes, resident immune cells, sensory nerve endings, and vascular signaling networks. Radiation-induced signaling may therefore remain local or potentially propagate through circulating metabolites, neural pathways, or migrating immune cells. Yet the detection of a skin response does not prove that sufficient mediator reaches a distant organ to change disease risk. Studies that combine local tissue sampling with circulating biomarkers and functional outcomes offer substantially stronger causal evidence than isolated transcriptomic measurements [1, 12, 13].

3.3. Experimental Design Implications

Wavelength, spectral irradiance, dose, exposed surface area, anatomical site, pigmentation, age, season, and recent exposure history should be reported explicitly. Sham irradiation and thermal controls are essential when the proposed mechanism is photochemical rather than heat-mediated. Investigators should also distinguish immediate photorelease, which may occur within minutes, from transcriptional responses requiring hours or repeated exposure. Failure to separate these timescales may obscure the relationship between the measured mediator and the clinical outcome [7, 8].

3.4. Photochemical Specificity and Interpretation

An exposure labeled “sunlight” contains multiple physical signals. Irradiance, wavelength, exposure duration, season, altitude, cloud cover, skin pigmentation, clothing and body surface area all modify the delivered dose. The biological response to retinal daylight cannot be inferred from an experiment using isolated UVB, and an effect of laboratory UVA cannot automatically be generalized to ordinary outdoor exposure. In addition, many epidemiological proxies, including latitude and time outdoors, simultaneously capture physical activity, ambient temperature, occupational status and socioeconomic factors. These distinctions are essential when attributing a systemic phenotype to a particular photoproduct rather than to the broader environmental context [1, 3, 9].

3.5. Local Versus Systemic Mediation

The first mechanistic question is whether the candidate mediator is generated in an irradiated tissue, transported into circulation, or acts locally to initiate a secondary endocrine or neural response. The second is whether its concentration reaches a biologically effective range at distant organs. Finally, a causal model should establish temporal ordering, dose responsiveness and reversibility through receptor antagonism, genetic manipulation or controlled exposure. Without such evidence, an observed biomarker change remains a correlate rather than proof of systemic mediation [7, 8, 12, 16]. The major sunlight-responsive bioactive mediators, their photochemical origins, downstream signaling pathways, and current clinical relevance are presented in Table 2.

Table 2: Photochemically responsive mediators: molecular source, downstream signaling, and clinical maturity

Mediator / pathway	Source and trigger	Downstream biological action	Human evidence / key uncertainty	Refs
NO, nitrite and nitrosothiols	Pre-existing cutaneous stores; UVA-dependent photorelease	Vascular smooth-muscle relaxation and altered hemodynamics	Acute human physiology demonstrated; long-term outcome effect unknown	7–10
POMC-derived β-endorphin	UV-responsive keratinocyte POMC processing	Opioid receptor signaling; proposed neurobehavioral effects	Human cutaneous expression and animal systemic responses; systemic human relevance unresolved	12,13,20
α-MSH / melanocortins	Cutaneous POMC processing after UV exposure	Melanogenesis and local immune signaling	Local effects established; independent systemic therapeutic effects not shown	20,21
Cis-urocanic acid	Trans-to-cis photoisomerization in epidermis	Immunomodulatory signaling after UV exposure	Predominantly mechanistic; may contribute to immunosuppression rather than net benefit	20,21
FICZ / AhR	Photoactive tryptophan-derived ligands; UV-sensitive signaling	AhR-dependent transcription, barrier and immune responses	Experimental and translational evidence; ligand- and context-dependent outcomes	18,19
IL-10 and related cytokines	UV-altered epidermal and immune-cell responses	Regulatory immune networks and inflammatory signaling	Clinical benefit cannot be inferred from cytokine induction alone	20,21
PGE2 / inflammatory lipids	UV-driven arachidonic-acid signaling	Vasodilation, inflammation and immune effects	Local biology established; responses may be harmful or protective	20,21
Melanopsin pathway	Visible light detected by retinal ipRGCs	Neural entrainment of central circadian networks	Strong mechanistic evidence; not a skin-derived circulating mediator	5,6,15
Mitochondrial / redox photobiomodulation	Visible/near-infrared exposures under selected experimental protocols	ROS/redox and transcriptional signaling	Protocol-specific laboratory findings; ordinary sunlight benefit cannot be assumed	22

Notes: "Photoinduced" includes release, isomerization, signaling activation and expression changes; it does not always mean *de novo* synthesis. The cited review articles summarize multiple primary experiments and should be supplemented with individual original studies during reference expansion.
Abbreviations: AhR, aryl hydrocarbon receptor; FICZ, 6-formylindolo[3,2-b]carbazole; IL, interleukin; ipRGC, intrinsically photosensitive retinal ganglion cell; NO, nitric oxide; PGE2, prostaglandin E2; POMC, proopiomelanocortin; ROS, reactive oxygen species; UV, ultraviolet.

4. Cutaneous Nitric Oxide and Vascular Physiology

The skin contains nitrite, nitrosothiols and other photolabile nitrogen oxide pools. Opländer and colleagues showed that whole-body UVA irradiation could release nitric oxide-related bioactivity and lower systemic blood pressure [7]. In a controlled human study, Liu and colleagues reported UVA-associated arterial vasodilation and blood-pressure lowering independent of nitric oxide synthase activity, consistent with mobilization of pre-existing cutaneous stores [8]. These studies support a rapid photochemical mechanism rather than new enzymatic synthesis of NO.

The clinical significance remains unsettled. A 2019 systematic review found inverse associations between sunlight/UV exposure and blood pressure in several observational studies, but heterogeneous exposure measures prevented quantitative pooling [9]. A 2026 systematic review of 14 studies similarly found predominantly favorable short-term signals, alongside inconsistent findings and substantial design heterogeneity [10]. In contrast, a large observational analysis reported associations between longer outdoor light exposure and increased hypertension risk, underscoring that physiological experiments and epidemiology do not always agree [11]. No standardized UVA regimen has demonstrated long-term cardiovascular event reduction with an acceptable safety profile.

4.1. Nitrogen Oxide Reservoirs and Photolysis

Nitric oxide signaling is not confined to nitric oxide synthase activity. Human skin contains photolabile nitrogen oxide-related species, including nitrite and nitrosated compounds, that can be mobilized by irradiation. Opländer and colleagues reported reductions in systemic blood pressure after whole-body UVA exposure together with evidence supporting mobilization of cutaneous nitrogen oxide stores. This observation provides a mechanistic basis for rapid vascular responses without requiring a delayed endocrine pathway [7].

4.2. Human Experimental Confirmation

Liu and colleagues tested UVA irradiation in human volunteers and observed vasodilation and reductions in blood pressure alongside changes in circulating nitrogen oxide-related species. Importantly, the physiological interpretation was supported by evidence that the response did not require conventional nitric oxide synthase activation. These studies are stronger evidence for an acute physiological effect than ecological correlations between sunlight, latitude, and cardiovascular events [8].

4.3. Why Acute Blood-Pressure Reduction Is Not Clinical Prevention

A short-lived fall in blood pressure is not equivalent to a sustained reduction in hypertension, myocardial infarction, stroke, or mortality. Differences in baseline vascular function, skin phenotype, irradiation protocol, and concomitant medications could modify response. A systematic review of sunlight, blood pressure, and cardiovascular outcomes highlighted the limitations of observational and intervention evidence, while a later synthesis found heterogeneity across ultraviolet blood-pressure experiments. Conversely, some observational data link greater outdoor light exposure to higher blood pressure, underscoring the hazards of simplistic causal interpretations [9-11].

4.4. Future Vascular Trials

The most informative trials would randomize participants to wavelength-defined irradiation and appropriate controls, record ambulatory blood pressure, assess vascular reactivity and nitrogen oxide metabolites, and monitor skin safety.

Repeated exposure studies would clarify whether vascular adaptation persists or attenuates. Trials should not presume that increased UV exposure is a desirable intervention merely because a molecular pathway is plausible [7-11].

4.5. Clinical Relevance and Unresolved Mechanistic Questions

The photomobilization of cutaneous nitrogen oxide stores provides a biologically plausible explanation for the acute vasodilatory responses observed following controlled UVA irradiation in humans [7, 8]. Nevertheless, several mechanistic and translational questions remain unresolved, including the relative contributions of individual photolabile nitrogen species, their transport into the systemic circulation, the influence of skin phenotype and exposed surface area, and the persistence of vascular responses following repeated irradiation. Importantly, transient reductions in blood pressure do not establish long-term protection against hypertension or cardiovascular events. Conflicting observational findings further emphasize the need for wavelength-specific, adequately controlled human studies that integrate molecular measurements, ambulatory blood pressure, endothelial function, and cumulative ultraviolet safety [9–11].

5. Epidermal POMC, Melanocortins and Beta-Endorphin

UV exposure activates keratinocyte stress pathways and can increase expression of proopiomelanocortin (POMC), the precursor of melanocortin peptides and beta-endorphin. In a mouse model, Fell and colleagues found that repeated UV exposure increased circulating beta-endorphin and altered nociceptive and reward-related behaviors; these observations should not be presented as evidence that sun exposure treats human chronic pain [12]. A small human skin study found increased epidermal beta-endorphin immunostaining after narrowband UVB exposure, establishing local biological responsiveness but not systemic analgesic efficacy [13].

Alpha-melanocyte-stimulating hormone participates in pigmentation and local immune signaling. The POMC axis illustrates the distinction between synthesis of a bioactive mediator and clinically meaningful systemic benefit. It also illustrates a potential adverse consequence: rewarding effects might reinforce excessive UV-seeking behavior.

5.1. The Epidermal POMC Axis

Ultraviolet exposure can activate keratinocyte stress-response pathways and alter proopiomelanocortin processing. This precursor gives rise to melanocortin peptides involved in pigmentation and to beta-endorphin, an endogenous opioid peptide. These products should not be treated as interchangeable: melanocortin signaling participates in epidermal adaptation, whereas opioid signaling may affect nociception and behavior. The degree to which cutaneous production generates systemic effects depends on tissue compartment, concentration, clearance, and receptor access [12, 13].

5.2. Preclinical Behavioral and Nociceptive Evidence

Fell and colleagues demonstrated that repeated UV exposure in mice increased circulating beta-endorphin and produced opioid-dependent changes in nociceptive thresholds and behavior. The experimental use of knockout models and pharmacological antagonism strengthened mechanistic inference. However, rodent responses cannot be assumed to predict clinically useful analgesia or mood improvement in humans. Indeed, the same findings raise concerns about reinforcement of excessive UV-seeking behavior [12].

5.3. Evidence in Human Skin

A small in-vivo human study demonstrated increased epidermal beta-endorphin immunostaining after narrow-band UVB exposure. The result supports a local cutaneous response, but did not establish a corresponding increase in circulating peptide, clinically meaningful analgesia, or improvement in depressive symptoms. Larger controlled studies would need paired tissue and plasma measurements, blinded functional outcomes, and careful assessment of exposure risk [13].

5.4. Clinical Interpretation

The POMC pathway is an excellent example of why mechanistic novelty should not be presented as a therapeutic recommendation. Endogenous opioid signaling could have beneficial or adverse consequences depending on context. At present, the evidence is more compelling for UV-responsive peptide biology than for deliberate solar exposure as a treatment for chronic pain or psychiatric disorders [12, 13].

5.5. Systemic Significance of Cutaneous Neuropeptide Signaling

The POMC pathway illustrates how ultraviolet radiation may connect epidermal stress responses with neuroendocrine signaling beyond pigmentation. Although melanocortins and β-endorphin originate from a common precursor, their biological actions, tissue distribution, and potential systemic consequences differ substantially. Experimental evidence supports UV-responsive opioid signaling, including altered nociceptive and reward-related behavior in rodents, while human studies demonstrate local epidermal β-endorphin expression following narrowband UVB exposure [12, 13]. However, the extent to which these cutaneous responses influence circulating peptide concentrations, central nervous system activity, or clinically meaningful pain outcomes in humans remains uncertain. The potential reinforcement of excessive UV-seeking behavior also highlights the need to evaluate adverse consequences alongside proposed neurobehavioral benefits.

6. Photoimmunology and Immunoregulatory Signaling

UV radiation can alter antigen presentation, inflammatory cytokine release and local immune tolerance. Photoisomerization of epidermal trans-urocanic acid to cis-urocanic acid is a classical candidate mechanism for UV-associated immunomodulation. UV-induced immune signaling is context dependent: IL-10 and regulatory pathways may suppress inflammatory responses, whereas oxidative injury, inflammatory eicosanoids and tissue damage can promote pathology. Thus “immunosuppression” is not synonymous with “immune health.”

The relevance to autoimmune disease is particularly nuanced. Photosensitive lupus can be exacerbated by UV exposure, making broad advice to seek UV for immunomodulation inappropriate [14]. Epidemiological associations between ambient sunlight and autoimmune disease incidence require separation from individual UV dose, behavior, genetic susceptibility and disease-specific mechanisms. Controlled

phototherapy should not be conflated with unmonitored sunlight.

6.1. Local and Systemic Immune Communication

Ultraviolet irradiation can alter antigen presentation, cytokine expression, immune-cell trafficking, and regulatory networks within the skin. These processes are relevant to both therapeutic phototherapy and the suppression of anti-tumor immune surveillance. The same pathway may therefore be useful in a localized inflammatory disease and undesirable in the setting of carcinogenesis. Immunomodulation should be described neutrally until the direction of clinical benefit is established [1, 14].

6.2. Regulatory Mediators and Context Dependence

Proposed participants include IL-10, prostaglandins, melanocortin-related pathways, and photochemically modified epidermal molecules. Mechanistic models must distinguish changes in expression from functional immune suppression, and local from systemic effects. Moreover, immunological endpoints depend on dose, timing, skin condition, and the pre-existing inflammatory milieu. A cytokine increase measured after irradiation cannot alone support a conclusion about prevention of autoimmune disease [1, 14].

6.3. Autoimmune Disease AND Photosensitivity

Observational associations between sunlight and autoimmune disease occurrence are difficult to interpret because outdoor behavior, geography, infection exposure, and other environmental determinants covary. Particularly in lupus erythematosus, UV exposure can aggravate cutaneous disease and may be clinically hazardous. This creates a central translational tension: phototherapy can be effective in selected skin disorders, but extrapolation to systemic autoimmune disease requires disease-specific evidence and risk assessment [14, 17].

6.4. A Framework for Immune Causality

A persuasive translational sequence would show a reproducible UV-induced mediator, demonstrate its appearance in a biologically relevant compartment, establish receptor or pathway engagement, and finally identify a patient-important outcome. Interventional blocking experiments can strengthen mechanism; randomized trials are necessary to establish clinical benefit. This hierarchy helps prevent overinterpretation of attractive molecular hypotheses [1, 14].

6.5. Therapeutic Opportunities and Immunological Trade-Offs

The immunological consequences of solar radiation depend on wavelength, dose, tissue environment, and underlying disease. UV-induced regulatory pathways may contribute to the therapeutic effects of controlled phototherapy in selected inflammatory dermatoses, but these responses coexist with potentially unfavorable consequences, including impaired cutaneous immune surveillance and exacerbation of photosensitive disorders such as lupus erythematosus [14, 17]. Future studies should establish whether specific photoproducts or immune mediators are necessary for the observed effects, determine their local and systemic bioavailability, and assess clinically meaningful outcomes rather than isolated changes in cytokine expression. This approach may help identify therapeutic targets capable of reproducing favorable immunomodulatory effects without unnecessary ultraviolet exposure [20, 21, 23].

7. Retinal Photoreception, Circadian Timing and Sleep

Among the most established systemic actions of natural light is entrainment of circadian rhythms through the retina. Hattar and colleagues characterized melanopsin-containing retinal ganglion cells projecting to circadian centers [5], while Berson and colleagues demonstrated intrinsic light sensitivity in these cells [6]. Light timing, intensity and spectral distribution influence circadian phase and alertness. Daylight exposure during the biological day may support robust day–night contrast, whereas light at inappropriate circadian times can disrupt sleep.

The relationship between habitual personal light exposure, sleep and mood is nevertheless more heterogeneous than laboratory photoreception data might suggest. A systematic review by Böhmer and colleagues found limitations in the quality and comparability of observational studies [2, 15]. Consequently, robust evidence for a light-sensing mechanism must be distinguished from certainty about any universal duration of outdoor exposure or treatment of mood disorders.

7.1. The Retinal Pathway Is Not A Skin-UV Pathway

Intrinsically photosensitive retinal ganglion cells expressing melanopsin provide environmental light information to circadian and other non-image-forming systems. Foundational anatomical and physiological studies established these retinal pathways and their capacity to influence the central biological clock. The implication is clinically important: daylight-mediated circadian effects generally do not require exposing skin to ultraviolet radiation [5, 6, 15].

7.2. Timing, Intensity, and Spectral Composition

The effect of light depends not only on intensity but also on timing relative to internal circadian phase. Morning light may support circadian alignment in some contexts, whereas light at biologically inappropriate times can delay timing and disturb sleep. Daytime exposure and evening light avoidance are therefore distinct behavioral questions. Studies that merely report total daily outdoor time may conceal these opposite temporal effects [2, 5, 6, 15].

7.3. Sleep, Alertness, and Mood

A systematic review of daily personal light exposure and sleep-wake rhythm or mood in healthy adults identified heterogeneous evidence and methodological limitations. This should temper claims that sunlight reliably treats depression or insomnia in the general population. Nevertheless, the retinal photoreception pathway itself is well established, providing a stronger biological foundation for circadian regulation than for many proposed systemic UV benefits [2, 5, 6, 15].

7.4. Clinical Opportunities Without Additional UV Burden

Circadian interventions can be developed using environmental daylight, window design, scheduling, and controlled light sources without assuming that unprotected UV exposure is necessary. Future trials should measure retinally relevant light exposure, circadian phase, objective

sleep outcomes, and adverse effects rather than rely solely on self-reported sunshine hours [2, 5, 6].

7.5. Clinical Implications of Retinal Light Signaling

Retinal photoreception represents one of the most clearly established pathways through which environmental light influences systemic physiology independently of cutaneous ultraviolet exposure. Its clinical relevance extends beyond circadian phase regulation to the organization of sleep–wake behavior, daytime alertness, and potentially mood-related outcomes [2, 5, 6, 15]. However, the effectiveness of habitual daylight exposure depends on individual circadian timing, spectral characteristics, exposure duration, and behavioral context. Future clinical investigations should therefore prioritize objective personal light dosimetry, circadian phase markers, actigraphy, and validated sleep outcomes. Importantly, these potential benefits can generally be pursued through appropriately timed visible-light exposure without deliberate ultraviolet irradiation.

8. Metabolic and Endocrine Pathways

Preclinical experiments suggest that UV can affect metabolic signaling beyond skin. Geldenhuys and colleagues reported attenuation of obesity and metabolic-syndrome features in high-fat-fed mice following UV exposure, with nitric oxide implicated in the response [16]. These findings are hypothesis-generating; animal photobiology, experimental dose and metabolic phenotype cannot establish that UV exposure prevents human obesity or diabetes. Light-dependent circadian organization may also influence metabolic timing, but this retinal mechanism is separate from cutaneous UV photochemistry.

Endocrine claims require similar precision. Cutaneous POMC signaling and central circadian regulation are demonstrable, yet changes in circulating hormone levels, clinical endocrine outcomes and causal mediation are not interchangeable. Studies should specify whether measured mediators originate in skin, endocrine organs or neural circuits.

8.1. Preclinical Metabolic Findings

Geldenhuys and colleagues reported that ultraviolet exposure reduced obesity-related and metabolic-syndrome features in mice fed a high-fat diet, with experimental findings implicating pathways beyond the conventional endocrine explanation. Such studies provide biological plausibility but do not establish efficacy in humans. Mouse fur, skin structure, irradiation protocols, and metabolic physiology differ from those of people, limiting direct clinical translation [16].

8.2. Potential Cross-Talk Among Systems

Metabolic responses may arise indirectly through vascular signaling, inflammatory pathways, autonomic physiology, circadian timing, or altered behavior. These mechanisms are difficult to separate in observational cohorts because people with greater daylight exposure may also differ in activity, sleep, work schedules, and dietary patterns. Mechanistic studies should use factorial designs where feasible and include objective measures of light, movement, and metabolic state [2, 9, 16].

8.3. Endocrine Interpretation

The skin has neuroendocrine-like signaling capabilities, but local peptide expression does not necessarily indicate systemic endocrine action. Circadian changes in melatonin are better understood as responses to retinal light input and the timing of darkness, not simply as increased hormone production during sunlight exposure. Claims of broad endocrine rejuvenation from solar exposure are therefore not supported by the cited mechanistic evidence [5, 6, 12, 13, 15].

8.4. Research Priorities in Human Metabolism

Proof-of-concept trials could evaluate insulin sensitivity, continuous glucose metrics, endothelial function, and inflammatory biomarkers while controlling for activity, temperature, and sleep. However, until controlled human benefits are demonstrated, experimental metabolic findings should remain hypothesis-generating and must not be used to justify unnecessary UV exposure [9, 11, 16].

8.5. Translational Challenges in Metabolic Photobiology

Experimental findings suggest that ultraviolet radiation may influence adiposity, glucose regulation, and inflammatory metabolism through pathways involving nitric oxide and other light-responsive mediators [16]. Nevertheless, these observations remain predominantly preclinical, and their relevance to human metabolic disease has not been established. A major translational challenge is distinguishing direct photochemical effects from indirect influences of circadian organization, physical activity, sleep, ambient temperature, and dietary behavior. Future human studies should integrate controlled spectral exposure, objective activity and sleep monitoring, metabolic biomarkers, and clinically relevant endpoints to determine whether sunlight-induced molecular responses confer measurable metabolic benefits independently of behavioral confounding [2, 9, 16].

9. Dermatological and Therapeutic Photobiology

Clinical phototherapy provides proof that precisely delivered radiation can modify disease activity. Narrowband UVB is an established treatment option for psoriasis; the LITE randomized trial evaluated home versus office administration of this controlled intervention [17]. Such evidence concerns selected patients, medical supervision, defined equipment and therapeutic protocols. It does not demonstrate that unrestricted sunbathing is equivalent or safe.

Photobiological responses are bidirectional. UV causes DNA damage, contributes to skin carcinogenesis and photoaging, and can worsen photosensitive conditions. The clinical question is therefore not whether UV has any beneficial molecular effects, but whether a specific exposure achieves a favorable net outcome relative to safer alternatives.

9.1. Controlled Phototherapy Versus Sunlight

Medical phototherapy differs from natural solar exposure in wavelength selection, dose reproducibility, supervision, and monitoring. This distinction is central to evidence interpretation: benefit demonstrated with narrow-band UVB cannot be assumed for unsupervised outdoor exposure. Clinical decisions require attention to cumulative dose, patient characteristics, photosensitizing medications, and malignancy risk [14, 17].

9.2. Psoriasis as an Example of Clinical Translation

The LITE randomized clinical trial compared home-based and office-based narrow-band UVB phototherapy for psoriasis, providing clinical evidence for a specific controlled modality. Its results inform access and delivery of phototherapy rather than demonstrating that routine sunbathing is an equivalent intervention. This is an instructive example of successful translation from photobiology to an evaluated treatment pathway [17].

9.3. Inflammation, Pigmentation, and Barrier Responses

Epidermal melanocortin and stress-response signaling are part of the skin adaptation to UV exposure, but pigmentation is not proof of protection against all radiation-related injury. UV-associated inflammation may involve prostaglandin and cytokine signaling; the same network that modifies inflammatory disease can also participate in photoaging and carcinogenesis. Consequently, mechanistic tables should classify both potentially favorable and harmful effects [1, 12, 14].

9.4. Clinical Phototherapy as a Controlled Intervention

Narrowband UVB and other medical phototherapies demonstrate that precisely specified wavelengths can produce clinically useful effects in selected dermatological conditions. Their controlled dosing, indication-specific protocols and surveillance distinguish them from unsupervised sun exposure. Evidence for therapeutic phototherapy cannot be transferred directly to general recommendations for ambient sunlight [8, 13].

9.5. The Dual Nature of Cellular Stress Responses

Radiation-induced reactive oxygen species and stress-response pathways can initiate adaptive signaling, including antioxidant and repair responses, while simultaneously causing inflammation, photoaging and DNA injury. Dose, wavelength and tissue vulnerability determine the balance. The existence of a potentially protective stress response does not negate established phototoxic and carcinogenic risks [1, 8, 13].

10. Cardiovascular Outcomes, Cancer and Mortality

Population-level outcomes are essential for evaluating the net balance of solar exposure. A 2025 systematic review by Parkhouse and colleagues identified 73 eligible reports, with 55 included in narrative synthesis. Findings for all-cause and cardiovascular mortality were mixed and frequently at high risk of confounding; higher sunlight exposure was generally associated with greater skin-cancer mortality in relevant studies [3]. These findings do not establish an optimal therapeutic UV dose and do not support abandoning photoprotection.

Cancer epidemiology is especially vulnerable to geographic and behavioral confounding. Latitude, physical activity, occupational exposures, access to care and screening behavior may all correlate with measured sunlight. A mechanistically plausible pathway cannot rescue an observational association from uncontrolled bias. Clinical recommendations must weigh known UV-related carcinogenic risks against benefits proven for a specific intervention.

10.1. Epidemiological Interpretation

Population studies sometimes associate sunlight exposure with cardiovascular or all-cause mortality outcomes, but exposure definitions and adjustment strategies vary substantially. Outdoor exposure may proxy for exercise, occupation, health status, latitude, climate, or socioeconomic position. Such associations should be interpreted separately from the short-term UVA vascular experiments that support a more specific physiological mechanism [3, 7-11].

10.2. Competing Outcomes and Risk-Benefit Balance

A physiological benefit in one system does not erase harm in another. UV radiation can damage skin and contribute to carcinogenesis, and immune suppression may facilitate tumor development. Any assessment of net health effects must consider competing outcomes, exposure accumulation, individual susceptibility, and the availability of safer methods to achieve the same goal [1, 3, 14].

10.3. Why a Universal Exposure Prescription Is Premature

Current evidence does not provide a validated UV dose that maximizes cardiovascular or immune benefit while minimizing dermatological risk across populations. Individual susceptibility, geographic conditions, and the specific wavelength required for each proposed effect complicate translation. The scientifically defensible conclusion is that pathways merit further study, not that more sun exposure is invariably healthier [3, 9, 10, 14].

10.4. What Observational Mortality Studies Can and Cannot Establish

The recent systematic review of sunlight exposure and mortality reported mixed associations across all-cause, cardiovascular and cancer outcomes, with substantial limitations related to exposure assessment and residual confounding. Mortality is a distant endpoint shaped by numerous environmental and behavioral determinants. Thus, even a reproducible association cannot establish that cutaneous nitric oxide, neuroendocrine peptides or any other individual photoproduct mediates the result [3].

10.5. Balancing Endpoints Rather than Selecting Favorable Outcomes

A balanced clinical interpretation must evaluate potential vascular or circadian advantages alongside the established hazards of excess ultraviolet radiation. Outcomes should be considered jointly, including skin cancer, photoaging, photosensitive disease, sleep disruption from poorly timed light and the possibility of behavioral overexposure. Evidence for one favorable intermediate marker does not imply that net population-level benefit exceeds cumulative risk [1, 3, 12, 14].

11. Neurological, Pain and Mental-Health Implications

Daylight affects alertness and circadian organization through retinal pathways, with downstream implications for sleep and mood [5, 6, 15]. Separately, skin-derived beta-endorphin has been proposed as a bridge between UV exposure and nociceptive or reward signaling [12, 13]. These lines of evidence should not be merged into a claim that UV treats depression, fibromyalgia or chronic pain. Human studies

directly linking UV-induced peptide changes to sustained symptom improvement are insufficient.

Future clinical studies could combine individual dosimetry, plasma and skin mediator measurements, circadian markers and validated patient-reported outcomes. They should also compare visible-light interventions with UV-containing interventions to determine whether the additional UV burden provides incremental benefit.

11.1. Separating Neurobiology from Clinical Outcomes

Light influences neural function through retinal circuits, while UV can activate skin-derived peptide pathways. These mechanisms differ in anatomy, latency, and risk. Their coexistence does not establish that UV exposure improves cognition, chronic pain, or mental health. Claims should identify the measured endpoint and whether the underlying evidence comes from human clinical trials, human tissue experiments, or animal models [2, 5, 6, 12, 13].

11.2. Pain-Related Findings

The rodent beta-endorphin experiment is mechanistically informative because the response was linked to opioid signaling. Nevertheless, it cannot be translated into a clinical analgesic recommendation without evidence of reproducible efficacy and safety in patients. In humans, demonstration of epidermal peptide expression is an intermediate biomarker rather than a validated pain outcome [12, 13].

11.3. Mood and Behavioral Confounding

People may report feeling better during sunny weather for reasons that include social interaction, physical activity, expectations, seasonal schedules, and circadian alignment. Rigorous studies should measure these variables and avoid attributing all changes to a single skin-derived molecule. The systematic light-exposure literature illustrates why promising associations can coexist with substantial uncertainty about effect size and causality [2].

11.4. Two Distinct Routes from Light to Brain

Light can affect the nervous system through retinal signaling and through candidate cutaneous mediators. Retinal pathways have direct experimental support for circadian regulation, whereas proposed skin-to-brain effects of β-endorphin and other peptides remain less clinically developed. These mechanisms should not be merged into a generic "sunlight increases serotonin" explanation, because different neurotransmitters, compartments and exposure conditions are involved [2, 5, 6, 12, 13, 15].

11.5. Implications for Chronic Pain Research

Pain outcomes are particularly vulnerable to expectation effects, activity changes and mood-related confounding. Experimental UV-associated nociceptive changes are scientifically interesting but do not establish analgesic efficacy in fibromyalgia, inflammatory arthritis or other chronic pain syndromes. A rigorous human study would require predefined pain endpoints, blinding where feasible, objective exposure measurement and separation of cutaneous signaling from changes in activity or sleep [12, 13].

12. Clinical Translation and Research Priorities

The strongest clinically actionable distinction is between access to daytime light for circadian signaling and deliberate UV exposure for cutaneous photochemistry. The former can often be pursued with skin protection; the latter requires a specific indication, exposure control and risk assessment. Patients with lupus, photosensitivity, skin-cancer risk or photosensitizing medication exposure warrant particular caution [14]. The clinical implications of these findings, including established physiological responses, unresolved therapeutic questions, methodological limitations, and priorities for future research, are summarized in Table 3.

Table 3: Clinical translation: what can be concluded, what cannot, and what should be measured next

Clinical question	Current conclusion	Most informative next study / measurement	Key confounder or safety issue	Refs
Can daylight improve circadian regulation?	Yes, retinal light is a major entrainment signal; real-world benefit varies with timing and dose.	Time-stamped personal light dosimetry; actigraphy; dim-light melatonin onset; randomized timing comparisons.	Shift work, sleep schedules, evening light exposure.	2,5,6,15
Can UVA-mediated NO lower cardiovascular risk?	Acute vasodilation demonstrated; clinical-event reduction not established.	Repeated-exposure randomized studies with ambulatory BP, NO metabolites and endothelial outcomes.	Temperature, drugs, skin phototype and cumulative UV injury.	7–10
Does UV improve autoimmune disease outcomes?	No general claim is justified; effects are disease- and exposure-specific.	Condition-specific controlled studies with immunophenotyping and disease activity endpoints.	Lupus photosensitivity, immunosuppression and photocarcinogenesis.	14,20,21
Can solar exposure prevent metabolic disease?	Animal results are hypothesis-generating, not human clinical proof.	Controlled human mechanistic trials with insulin sensitivity and spectral dosimetry.	Adiposity, exercise, temperature, diet and seasonal confounding.	16
Can UV-induced β-endorphin relieve chronic pain?	Human systemic analgesic efficacy is unproven.	Human exposure studies measuring circulating peptides alongside validated pain endpoints.	UV adverse effects and distinction between local peptide expression and systemic action.	12,13
Can phototherapy findings be generalized to sunlight?	No: prescribed spectrum and dose differ from uncontrolled environmental exposure.	Head-to-head spectral and dose-controlled comparisons where ethically justified.	Skin cancer risk, cumulative exposure and variable environmental irradiance.	17,22

Notes: The table intentionally separates demonstrated physiological mechanisms, therapeutic phototherapy, observational associations and unresolved hypotheses. No row recommends deliberate unprotected UV exposure.

Abbreviations: BP, Blood Pressure; NO, Nitric Oxide

Priority research questions include: (i) whether UVA-mediated NO changes persist with repeated exposure; (ii) whether any vascular response translates into hard outcomes; (iii) whether skin-derived peptides reach biologically effective systemic concentrations in humans; (iv) how UV-induced regulatory signaling differs by autoimmune diagnosis; (v) whether metabolic findings replicate in controlled human studies; and (vi) how individual pigmentation, age, season and ambient conditions modify benefit–risk relationships. Future trials should report wavelength, irradiance, cumulative dose, timing, skin phototype, concomitant medication and adverse outcomes.

Mediator-centered trial design: Future clinical research should move from broad labels such as "sunlight exposure" to reproducible interventions defined by spectrum, dose, timing, and target tissue. For nitric oxide, endpoints should include circulating nitrogen oxide-related species and ambulatory blood pressure; for retinal pathways, circadian phase and objective sleep; for immune pathways, validated cellular and clinical outcomes. Mechanistic endpoints and patient-important outcomes should be prespecified separately [2, 7-10, 14].

Population heterogeneity: Phototype, age, baseline vascular function, photosensitivity, immunosuppression, skin cancer history, and concomitant medications may influence the balance of effects. Studies should recruit diverse participants and report subgroup analyses cautiously. In autoimmune conditions, especially those with photosensitivity, safety should be built into the study design rather than treated as an afterthought [8, 14].

Non-UV alternatives. Where a benefit depends on retinal light signaling, daylight or appropriately designed artificial illumination may provide a pathway that avoids additional UV exposure. Where the putative mechanism requires UVA or UVB, clinical translation should first investigate whether the downstream mediator can be targeted more selectively. This approach preserves mechanistic innovation without assuming that broad-spectrum solar exposure is the optimal treatment [5, 6, 8, 15].

Evidence reporting standards. Narrative reviews should disclose search scope, selection principles, limitations, and potential conflicts. The SANRA framework is useful for ensuring that the manuscript articulates its rationale, searches responsibly, references central claims, and maintains coherent scientific reasoning. A structured narrative approach should not be mislabeled a systematic review or imply exhaustive database coverage that has not occurred [4].

A Hierarchy for Interpreting the Evidence

The strongest mechanistic claims are those supported by controlled exposure and pathway perturbation. Human physiological studies occupy a distinct level from epidemiological associations, and both differ from animal models. For each candidate mediator, the key translational sequence is: demonstrable photochemical change; reliable biomarker measurement; systemic bioavailability or neural signaling; reproducible target-organ response; and clinically meaningful benefit. Missing links should be reported explicitly rather than inferred [7, 8, 12, 16].

Toward Safer Photobiological Interventions

One promising direction is to identify pathways that can be activated without exposing large skin areas to carcinogenic radiation. Wavelength-selective illumination, circadian lighting strategies and pharmacological targeting of downstream mediators are conceptually distinct possibilities. Their efficacy and safety must be tested independently. For now, evidence supporting daytime visible light for circadian alignment should not be used as an argument for deliberate unprotected UV exposure [2, 5, 6, 14, 17].

Methodological Agenda

Future investigations should report calibrated spectral irradiance, cumulative dose, exposed body surface area, skin phenotype, time of day and environmental temperature. Trials should prespecify clinical outcomes, record adverse events and include sufficient follow-up to distinguish transient physiological changes from durable effects. In observational studies, objective dosimetry and careful adjustment for activity, occupation and socioeconomic variables are essential. Mechanistic studies should also evaluate whether a candidate mediator is necessary and sufficient for the reported response [3, 7–11, 16].

12.1. Photoactive Tryptophan Metabolites and Aryl Hydrocarbon Receptor Signaling

The conversion of endogenous chromophores into signaling ligands represents a distinct form of photobiology. Tryptophan-derived 6-formylindolo[3,2-b]carbazole (FICZ) is a high-affinity ligand of the aryl hydrocarbon receptor (AhR), a ligand-activated transcriptional regulator that integrates environmental sensing with xenobiotic metabolism, barrier biology, and immune differentiation. FICZ formation following photochemical reactions provides a plausible bridge between incident radiation and changes in gene transcription. However, its existence as a photoproduct does not establish that sunlight-driven AhR activation is uniformly protective; AhR effects vary by ligand, concentration, tissue, metabolic clearance, and inflammatory setting [18, 19].

Experimental studies have reported rapid AhR activation after cutaneous UV exposure, with evidence of signaling in tissues beyond the irradiated skin in animal models. This is conceptually important because it suggests that a locally generated ligand can behave as an endocrine-like messenger. The direct relevance to habitual human sunlight exposure, chronic disease prevention, and safe exposure thresholds remains unresolved. A rigorous interpretation therefore separates biochemical formation of a ligand, target engagement in experimental systems, and demonstrated clinical efficacy [19].

AhR also illustrates why a simple beneficial-versus-harmful dichotomy is inadequate. In keratinocytes and immune cells, ligand-dependent signaling can influence differentiation, barrier integrity, oxidative responses, and cytokine networks. A potentially favorable response in one disease model may be adverse in another. Studies that measure only downstream CYP1A1 expression should not be treated as proof of a

systemic health benefit. Future human investigations should measure exposure spectrum, circulating ligand or metabolites, tissue-specific target engagement, and prespecified physiological outcomes [18, 19].

12.2. Skin–brain Communication and Cutaneous Neuroendocrine Axes

The skin possesses an integrated neuro–immuno–endocrine apparatus containing sensory nerves, local steroidogenic machinery, melanocortin signaling, and mediators that communicate with immune and central regulatory systems. Ultraviolet radiation can activate stress-response pathways and alter local expression of corticotropin-releasing hormone-related signals, proopiomelanocortin-derived peptides, and inflammatory mediators. These findings support viewing the skin as an active environmental sensor rather than an inert surface [20, 21].

The physiological interpretation must distinguish a cutaneous response from an endocrine response in the bloodstream. Detection of a neuropeptide in epidermal tissue is not equivalent to a reproducible rise in systemic concentrations, and systemic concentrations do not necessarily demonstrate altered clinical outcomes. Similarly, rodent findings on UV-associated β-endorphin and behavioral reinforcement cannot be directly extrapolated to human analgesic treatment. This distinction is essential when discussing chronic pain, mood, or stress-related conditions [12, 13, 20].

The most defensible translational framework treats sunlight exposure as a multisite sensory input. Retinal light detection provides a direct neural route to circadian centers, whereas irradiated skin can generate humoral and peripheral neural signals. These pathways may converge on sleep, autonomic regulation, and immune function, but the magnitude and independence of each route in everyday human exposure are still incompletely characterized [5, 6, 20, 21].

12.3. Visible and Infrared Light: Mechanisms Beyond Ultraviolet Radiation

Visible and infrared radiation comprise a large proportion of solar energy reaching the body, yet their mechanisms cannot be inferred from ultraviolet studies. Visible light acts through retinal photoreception and also interacts with cutaneous chromophores and opsin-associated signaling. Infrared exposure involves substantial thermal effects; controlled red and near-infrared illumination has additionally been studied in photobiomodulation models. These experimental systems must not be equated automatically with unmeasured outdoor sunlight exposure [22].

Proposed photobiomodulation pathways include mitochondrial redox signaling, changes in reactive oxygen species at signaling concentrations, and downstream transcriptional responses. The literature is technically heterogeneous: wavelength, irradiance, fluence, pulse structure, tissue depth, and thermal control can substantially alter results. Accordingly, reports from specialized devices cannot establish that ordinary sunlight produces the same biological effect or that increasing solar exposure would improve a given condition [22].

Visible and infrared irradiation can also modulate cutaneous immune responses in experimental contexts. The direction of effect depends on wavelength and exposure protocol, with both pro-inflammatory and regulatory observations. An appropriate narrative synthesis should preserve the distinction between light-driven physiological signaling and a clinically validated treatment. The clearest established non-UV systemic pathway remains retinal light entrainment of the circadian system [5, 6, 8, 22].

12.4. Immunological Trade-Offs, Host Defense, and Autoimmune Disease

Ultraviolet exposure can modify antigen presentation, regulatory immune networks, and local cytokine expression. Such responses are sometimes framed as anti-inflammatory, but suppression of an immune response is not inherently beneficial. The same mechanisms that may contribute to therapeutic control of selected inflammatory dermatoses can interfere with immune surveillance and contribute to photocarcinogenesis. Interpretation requires specifying the immune compartment, clinical indication, and exposure context [20, 21, 23].

In autoimmune disorders, broad generalizations are especially problematic. Photosensitivity is a clinically important feature of lupus erythematosus, whereas ultraviolet-based phototherapy is an established controlled treatment option for selected inflammatory skin diseases. Observational associations between sunlight and incidence of autoimmune disease are vulnerable to latitude, behavior, occupational activity, and other confounders. The review should therefore avoid presenting sunlight as a generic immunological intervention for systemic autoimmune disease [14, 17, 23].

A research agenda should compare spectral exposures under controlled conditions, measure immunophenotypes before and after exposure, and determine whether molecular signatures translate into meaningful outcomes such as disease activity, infection risk, or treatment requirements. Until such evidence is available, immune mediators should be described as biological responses rather than established reasons to seek unprotected UV exposure [20, 23].

12.5. Epidemiological Associations and Causal Inference

Population studies linking outdoor light or ambient UV exposure with cardiovascular disease, infection, cancer, and mortality have generated hypotheses about systemic benefits. Nevertheless, an association with sunlight is not evidence that a specific photoproduct mediates the outcome. Outdoor activity, temperature, physical fitness, deprivation, seasonality, air pollution, and healthcare access may affect both exposure and disease risk. Moreover, ambient radiation estimates are imperfect proxies for individual skin dose [3, 24].

A recent narrative synthesis of cardiovascular, infectious, cancer, and mortality outcomes identified potentially favorable associations in several observational studies but emphasized residual confounding and established dermatological harms. Such findings should motivate mechanistic studies rather than direct changes in exposure recommendations. Controlled human experiments are strongest for acute physiological effects, while long-term clinical endpoints remain a major evidence gap [3, 9, 10, 24].

For future research, a triangulation approach combining controlled spectral exposure, biomarker measurement, longitudinal personal dosimetry, and carefully adjusted observational cohorts would improve causal interpretation. Trials should also record adverse cutaneous outcomes and stratify participants by skin phototype, photosensitivity, medication use, and relevant comorbidities [9, 20, 24].

12.6. Integrated Evidence Map and Translational Priorities

The candidate mediators can be grouped by their proximity to a causal clinical pathway. First, direct photochemical products include mobilized nitric oxide-related species, cis-urocanic acid, and photo-oxidized tryptophan metabolites. Second, inducible cellular signals include melanocortins, prostaglandins, cytokines, and stress-response enzymes. Third, sensory and neuroendocrine outputs include retinal melanopsin signaling and cutaneous neuropeptides. Each group requires different analytical methods, exposure controls, and standards of clinical validation [7, 8, 18, 20, 21].

Across these mechanisms, the central unresolved question is not whether light changes human biology—it clearly does—but which changes confer net clinical benefit under realistic exposure conditions. An effect on gene expression, blood pressure over minutes, or immune cell phenotype cannot be assumed to prevent chronic disease. Conversely, the absence of definitive long-term trials does not invalidate established photochemical mechanisms. Keeping these levels of inference separate improves scientific precision and prevents repetitive claims of benefit [9, 10, 20, 24].

The strongest next-generation studies will compare narrow spectral bands, quantify actual delivered dose, verify intermediate mediators, and measure clinically relevant endpoints while monitoring harm. Such work may eventually permit targeted therapies that exploit specific pathways without requiring uncontrolled exposure to carcinogenic radiation [20, 22, 23].

13. Strengths and Limitations

The principal strength of this narrative review is its integrated examination of sunlight-induced biological effects beyond vitamin D, combining molecular photochemistry, vascular physiology, neuroendocrine signaling, immunoregulation, retinal photoreception, and clinical evidence. By distinguishing controlled human experiments, preclinical investigations, and observational findings, the review provides a framework for interpreting the translational relevance of individual bioactive mediators. Its limitations include non-systematic study selection, incomplete coverage of subscription databases and gray literature, the absence of formal risk-of-bias assessment across all included studies, and substantial heterogeneity in radiation dosimetry and outcome measurement. Consequently, the review does not provide pooled effect estimates or establish definitive exposure recommendations. Bibliographic details, particularly for references 18, 19, and 23, require final source-level confirmation before submission.

14. Conclusions

Sunlight engages several biologically important pathways beyond its traditionally emphasized cutaneous role. Human evidence is most persuasive for retinal circadian photoreception and short-term UVA-associated vascular responses; epidermal peptide and immune effects are biologically credible but their systemic clinical consequences remain less certain. Metabolic protection and analgesia are predominantly experimental propositions. Given established UV hazards and mixed long-term observational outcomes, sunlight-related molecular effects should not be converted into generalized prescriptions for unprotected exposure. Mechanism-specific interventions and rigorous human outcome studies offer the most promising path forward.

Declarations

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