Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

HOW DIGITAL LIFE DISRUPTS CIRCADIUM RHYTHMS ANDTHE MICROBIOME TO PROMOTE ACNE

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DOI: https://doi.org/10.5281/zenodo.20824354

Keywords
Acne vulgaris; circadian rhythm; Cutibacterium acnes; blue light; dysbiosis; chronotherapy; postbiotics

Article History
Received: 24 April 2026
Accepted: 03 June 2026
Published: 21 June 2026

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Abstract

The multifactorial inflammatory skin disorder Acnes vulgaris has a significant association with increased digital screen time, resulting in increasing prevalence in adults. Two new disruptors have emerged: digital light-induced circadian misalignment, and cutaneous microbiome dysbiosis. This review integrates mechanistic connections between exposure to blue light, clock gene dysregulation and changes in Cutibacterium acnes phylotypes in the pathogenesis of acne. Smartphone, tablet, and computer light, especially blue and near-ultraviolet light, inhibits nocturnal melatonin discharge through intrinsically photosensitive retinal ganglion cells and directly elevates the expression of the CLOCK and BMAL1 genes in sebocytes, augmenting lipogenesis and toll-like receptor 2-mediated inflammation. At the same time, circadian disruption leads to a decrease in antimicrobial peptides like LL-37 and human 2-defensin, allowing pro-inflammatory C. acnes phylotypes IA1 and IA2 to develop biofilms, and commensal phylotypes II and III to decrease. There is a gap in knowledge: there is no treatment that is currently able to treat the three components of digital hygiene, circadian restoration, and microbiome modulation together. This review thus examines clinically-approved and pipeline therapies to these pathways, such as chrono-pharmacology (timed low-dose isotretinoin, evening doxycycline), melatonin agonists (ramelteon), digital interventions (blue-blocking glasses, dynamic screen filters), and microbiome-directed treatments (C. acnes-specific bacteriophages, postbiotics A combination of chronobiology and microbiome restoration is a new potentially curative paradigm but phase III studies of dim light melatonin activation, skin metagenomics, real time light exposure are urgently required.

1.Introduction

The last ten years have seen an increase in average daily screen time to over ten hours per day in adults and adolescents with a significant proportion of this time being spent in the evening and nocturnal hours. This online culture has followed an trends of bewildering epidemiology: acnes vulgaris, a condition thought to be an adolescent one, is being increasingly diagnosed in adults, twenty-five years of age and above, and especially in women. Although traditional risk factors like nutrition, stress, and hormonal changes are still pertinent, they do not justify the sheer size of adult acne in cohorts that have a high level of digital device usage(Yang et al., 2023). Conventional therapies such as topical retinoids, systemic antibiotics, oral contraceptives and isotretinoin act against sebum production,

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ISSN: (e) 3007-1607 (p) 3007-1593

follicular hyperkeratinization, bacterial colonization, and inflammation. But none of these interventions is related to the contemporary trigger in the environment of the exposure to the artificial light in the night.

1.1 Cutaneous Circadian Machinery and Its Role in Skin Homeostasis

The skin has a complete peripheral circadian system, sebocytes, keratinocytes, and fibroblasts express core clock gene, such as PER1, PER2, CRY1, CRY2, CLOCK, and BMAL1. These genes do not only control sebum production and desquamation, but also control production of antimicrobial peptides and local immune tone(Hassan et al., 2025). Moreover, the cutaneous microbiome, specifically cutibacterium acnes shares a diurnal variation that is interrupted by circadian disruption(Tricarico et al., 2022). This review thus hypothesizes and supports the idea of a circadian-microbiome-acnes axis, investigating how digital life is disrupting this axis, exploring the current and emergent therapies that target this axis, and determining the gaps that need to be bridged to achieve a complete cure(Oliveira, Maurício, Barros, & Botelho, 2025).

2.The Circadian-Microbiome-Acne Axis

2.1Circadian Control of Antimicrobial Peptides and the Skin Microbiome

The balance in healthy skin is maintained with the skin's circadian clock and what happens when this clock goes wrong, causing acne(Tzenios, 2024 #97. In normal skin, sebocytes - the cells that produce oil within sebaceous glands - have clock genes including CLOCK, BMAL1, PER1 and CRY2 that fluctuate in a daily pattern so even in darkness, sebocytes have an idea of what time of day it is. At night, melatonin, which is produced in the pineal gland of the brain as well as locally in skin cells called keratinocytes, binds to MT1/MT2 receptors on sebocytes, which turns off lipogenesis (the making of new oil) and decreases oxidative stress (cell damage caused by reactive molecules)(Xavier-Souza et al., 2025). At the same time, the clock genes PER1 and CRY2 are highest during the night and CLOCK and BMAL1 highest during the day, defining a day-night cycle within the sebocytes themselves(Naharro-Rodriguez, Bacci, Hernandez-Bule, Perez-Gonzalez, & Fernandez-Guarino, 2025). This means sebum production is lowest at night during sleep, and highest in the late morning, which is the natural way of things and minimises the risk of clogged pores during sleep. At the same time, antimicrobial peptides like LL-37, human β-defensin 2, and psoriasin, are released with a circadian rhythm, with their highest levels in the early morning hours when bacterial growth kicks into gear - a clever immune response that ensures that the most potent anti-bacterial response is delivered at the right time as bacteria are preparing to multiply(Fernando Bernall, 2025).

2.2 The Vicious Cycle of Circadian Dysfunction, Inflammation, and Acne

The skin-friendly, commensal phylotypes of C. acnes, especially phylotypes II and III, have adapted to resist these antimicrobial peptides and help the skin barrier by producing short-chain fatty acids and maintaining a slightly acidic skin environment to prevent harmful bacterial growth. On the other hand, the inflammatory phylotypes IA1 and IA2 are normally suppressed by the circadian environment. But if circadian rhythms are thrown off, as by exposure to blue light at night, shift working or poor sleep, the balance is upset(Halioua et al., 2021). Suppression of melatonin allows increased sebum (oil) production, while clock gene dysfunction no longer stimulates secretion of antimicrobial peptides, which act as antibiotics on the skin(Buckingham, 2024). As a result, pathogenic strains of C. acnes (IA1 and IA2) proliferate, form slippery biofilms that are resistant to antibiotics and immune cells, and activate TLR2-dependent inflammation, which releases IL-1β and TNF-α, producing red bumps. Crucially, this pathway is a vicious cycle; the inflammatory cytokines also suppress clock gene expression, leading to a vicious cycle of blue more clock gene suppression, which causes more acne(K. W. A. Lee et al., 2024).

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2.3 Biofilm Formation: Why Antibiotics Fail in Acne

The pathogenic phylotypes IA1 and IA2 take full advantage of this opportunity in a big way. They multiply with gusto, and more importantly, they start to make biofilms. Biofilms are three-dimensional, ordered populations of bacteria embedded in a matrix of extracellular polysaccharides, proteins and DNA. Biofilms are not simply planktonic bacteria (those that are free-floating) in a different state(Mahendra et al., 2022). Biofilm bacteria use quorum sensing to "talk" to each other, sending and receiving signals to coordinate their behaviour. Bacteria exchange nutrients via channels through the matrix, spread antibiotic resistance genes via horizontal gene transfer, and protect each other from harmful environmental factors. The matrix prevents antibiotics from penetrating to the bacteria, so a typical course of treatment with doxycycline or minocycline (or even topical clindamycin) may not be effective(Djordjevic, Archer, Mohamed, & Kyprianou, 2025). The matrix also blocks the immune cells (neutrophils) from eating up the bacteria, because the bacteria are protected and because the matrix can destroy the antibodies and "complement" proteins that mark the bacteria for destruction(Hong et al., 2022). Once established on the skin surface or inside a hair follicle, biofilms are very resistant to killing, hence the persistence of acne despite multiple rounds of systemic and topical antibiotics over a period of years or even decades(Gupta, Suk, & Kim, 2021).

2.4 TLR2-Mediated Inflammation and Clinical Symptoms of Acne

The inflammatory effects of the biofilms are devastating and lead to the symptoms of acne. The biofilms interact with a surface receptor on immune cells such as macrophages, monocytes and dendritic cells called the Toll-like receptor 2 (TLR2). TLR2 is able to bind to molecular patterns on bacterial cell walls, such as lipoproteins and lipoteichoic acids(El-Baz, El-Sayed, Shetaia, & Abaza, 2025). Activation of TLR2 by elements of the C. acnes biofilm leads to a series of intracellular signalling events involving adaptor proteins such as MyD88, which then activate transcription factors such as NF-κB and AP-1. These factors translocate to the nucleus and activate the expression of genes for the inflammatory cytokines interleukin-1 beta and tumor necrosis factor-alpha(Tricarico et al., 2022). The cytokines are released by the immune cells and have far-reaching effects. They trigger the signs of inflammation: redness (due to increased blood flow as capillaries open up so immune cells can enter the tissue); swelling (due to the leakage of fluid from blood vessels into the tissues); heat (due to increased metabolic activity of the immune cells as they attempt to eliminate the infection); and pain (due to the activation of pain receptors in the skin by inflammatory factors)(Jovanovic, Sudhakar, & Knezevic, 2022). In acne, this is seen in the red bumps (papules), pus-filled bumps (pustules) and in very severe cases, the large, painful, deeper bumps (nodules and cysts) that can scarring. Patients not only report cosmetic and psychological issues but also pain, tenderness and even disfiguring scarring(Singh, 2023).

2.5 The Self-Perpetuating Nature of Chronic Acne

The concept of a vicious cycle, which is possibly the most important piece to understanding why acne is chronic and self-sustaining, rather than self-resolving or readily treatable(Osborne, 2022). The cytokines of inflammation, such as IL-1β and TNF-α, not only produce visible acne lesions, but also feed back to downregulate clock gene expression(Buckingham, 2024). This has been shown in several peer-reviewed papers in cell culture and animal models. This combination results in a double whammy for cutaneous balance: more food for bacteria (sebum) and less immune cells (CD4 T cells) to keep the bacteria in check(Mahendra et al., 2022). The pathogenic phylotypes IA1 and IA2 really capitalise on this opportunity. They grow like crazy, and even better, they start to produce biofilms. Biofilms are highly-structured populations of bacteria that are encased in a matrix of extracellular polysaccharides, proteins and DNA(Angel, 2021). Biofilms are not just planktonic (free-floating) bacteria, with a different life stage. Biofilm bacteria communicate with each other via quorum sensing, exchanging

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information(Simon et al., 2025). Bacteria share nutrients through the channels in the matrix, and share antibiotic resistance genes through horizontal gene transfer. The bacteria also protect each other against environmental stresses(Lombardi et al., 2024). The matrix blocks antibiotics from getting to the bacteria, so a standard course of antibiotics (doxycycline, minocycline or even topical clindamycin) may be ineffective. The matrix also prevents immune cells (neutrophils) from ingesting the bacteria because the bacteria are protected and because the matrix can inactivate antibodies and "complement" proteins that would usually tag the bacteria for ingestion(Neto, Leite, De Rossi, & Bonamigo, 2023). Once formed on the skin or within a hair follicle, biofilms are very difficult to kill, hence the recurrence of acne despite repeated courses of systemic and topical antibiotics over many years or decades. The biofilms cause terrible inflammation and this is what results in acne symptoms(DaSilva, Robinson, Shi, & McCauley, 2022). The biofilms bind to a molecule on the surface of immune cells such as macrophages, monocytes and dendritic cells called the Toll-like receptor 2 (TLR2). TLR2 can recognise patterns on the bacterial cell wall such as lipoproteins and lipoteichoic acids(Abraham, 2025). Stimulation of TLR2 by components of the biofilm of C. acnes results in a cascade of events inside the immune cells involving adaptor proteins such as MyD88, which then activate transcription factors such as NF-κB and AP-1(Nascimento et al., 2024). These migrate to the cell nucleus and switch on genes for the inflammatory cytokines interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α). These cytokines are secreted by the immune cells, and have profound effects(Hammer, 2023). They produce the symptoms of inflammation: redness (due to increased blood flow as capillaries open up so immune cells can enter the tissue); swelling (due to the leakage of fluid from blood vessels into the tissues); heat (due to increased metabolic activity of the immune cells as they attempt to eliminate the infection); and pain (due to the activation of pain receptors in the skin by inflammatory factors). In acne this is as red bumps (papules), pus-filled bumps (pustules) and in severe acne, the large, painful, deeper bumps (nodules and cysts) that can scarring(Tricarico et al., 2022). Acne patients not only report cosmetic and psychological distress but also pain, tenderness and even scarring. The vicious cycle, which is perhaps the most important aspect of acne and why it is a chronic self-sustaining rather than self-limiting or easily treatable condition(Rajan, 2024). The cytokines of inflammation, such as IL-1β and TNF-α, cause acne lesions, but also downregulate the clock genes. This has been demonstrated in a number of peer-reviewed publications in cultured cells and in animals(Gregg, 2024).

Table 1. ***Key Clock Genes in Human Sebocytes and Their Acne-Related Functions***

Gene	Role in skin	Effect of blue light / circadian disruption	Acne phenotype
CLOCK	Sebum synthesis	Upregulated (via ROS/NF-κB)	↑ sebum, ↑ comedo formation
BMAL1	AMP transcription	Downregulated (phase shift)	↓ LL-37, ↑ *C. acnes* load
PER1	Lipid peroxidation	Suppressed (nocturnal)	↑ squalene oxides → inflammation
CRY2	Melatonin receptor crosstalk	Desynchronized	↑ TLR2 activation

In Fig 1. This is showing that the vicious cycle, beginning with blue light suppressing melatonin, increasing CLOCK and BMAL1, increasing sebum, decreasing antimicrobial peptides, switching C. acnes from commensal to pro-inflammatory biofilms, and how cytokines further disrupt clock genes, creating a self-fulfilling cycle of blue light leading to clock disruption, to acne, to inflammation, to more clock disruption and so on.The result is a deadly combination for skin

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ISSN: (e) 3007-1607 (p) 3007-1593

homeostasis: increased availability of food for bacteria (sebum), and reduced availability of immune cells (CD4 T cells) to control bacterial proliferation (Knaggs & Lephart, 2023).

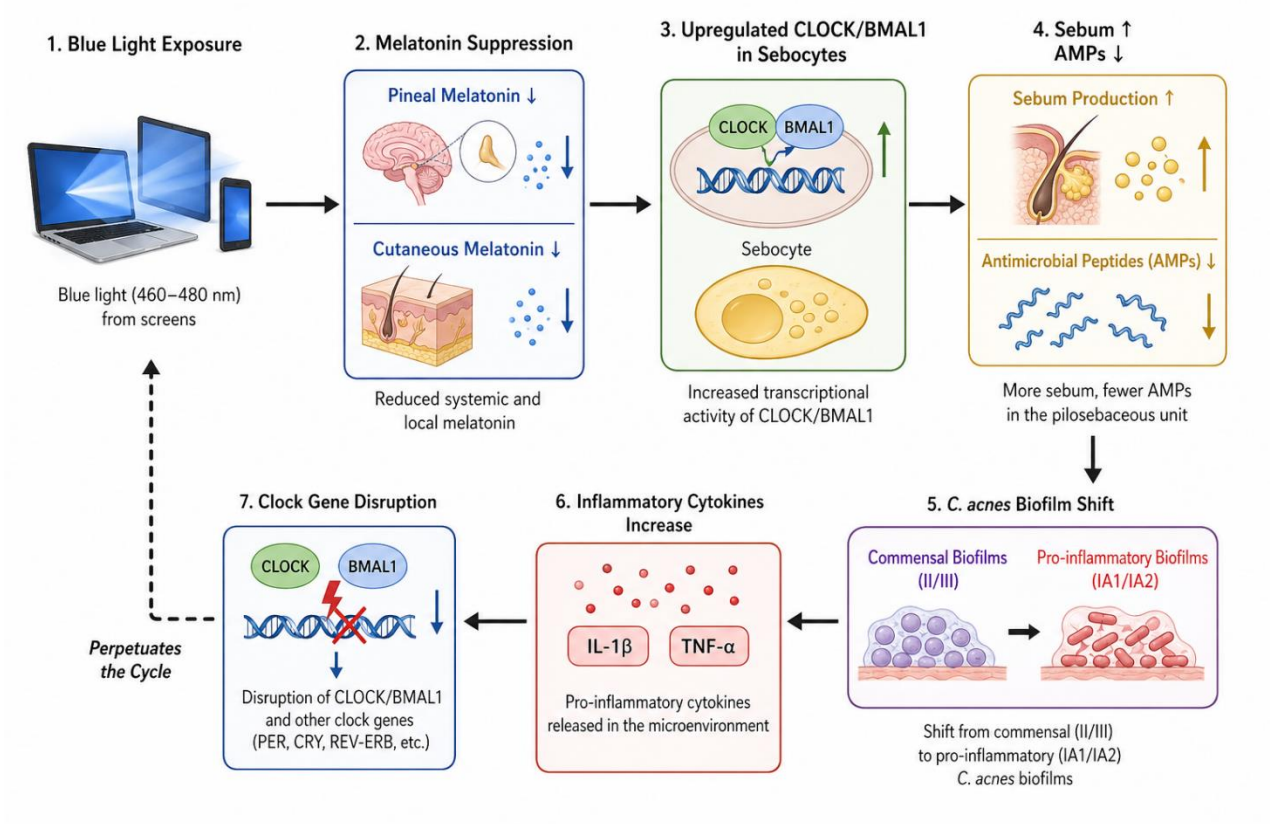

Figure 1. ***Vicious cycle, beginning with blue light suppressing melatonin, increasing CLOCK and BMAL1***

The main pathway is through intrinsically photosensitive retinal ganglion cells that have melanopsin that send a signal to the suprachiasmatic nucleus to suppress pineal melatonin production(Discepolo, 2024). Even exposure of a tablet or smartphone of a half an hour or two at the usual viewing distances can cut nocturnal melatonin by a fifth to a quarter. But the skin itself is also directly photosensitive(Géhin, Tokarska, Fowler, Barran, & Trivedi, 2023). In humans, the sebocytes produce opsin-3 which is a photopigment that reacts to blue light by creating reactive oxygen species and nuclear factor kappa-B. This signaling cascade increases the expression of CLOCK and BMAL1, which increases the expression of lipogenic genes such as SREBP-1c and fatty acid synthase(Naharro-Rodriguez et al., 2025).

In cell culture, exposure to blue light of SZ95 sebocytes in vitro for four hours enhances sebum secretion by about forty percent. Moreover, the use of nocturnal screens increases cortisol through stress pathways and sleep disturbance and cortisol itself is a strong sebocyte stimulant. The melatonin pattern of shift workers and individuals with a habit of screen time after midnight are flattened or phase-shifted, daytime cortisol levels are higher, and moderate-to-severe acne is two to three times more common than in persons with normal sleep-wake rhythms(SANDUA, 2024). This would be accompanied by [Diagram 2] depicting a schematic of a sebocyte nucleus whereby blue light would cause activation of opsin-3 → ROS → NF-kB → CLOCK and BMAL1 upregulation or inhibition of melatonin mitigation of PER1/CRY2, respectively, leading to higher SREBP-1c, FASN and lower DEFB4, CAMP.

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3. How Digital Life Disrupts Skin Circadian Rhythms

Digital screens damage the skin in two parallel pathways: one through the eyes and brain, and the other by directly affecting the skin, both leading to acne. Electronic screens produce blue light in the wavelength range of 430 to 480 nanometers and this particular range of light is highly effective at quelling melatonin, the hormone that induces drowsiness(Khosla, 2022). The main pathway starts in the eyes, where certain cells (intrinsically photosensitive retinal ganglion cells) have a photopigment (melanopsin)(Lucock, 2022). Exposure to blue light activates these cells, which communicate with the suprachiasmatic nucleus (the body clock) in the brain and signal the pineal gland to cease producing melatonin(Taylor, 2025). Indeed, even brief exposures of only 30-120 minutes from a tablet or smartphone at normal reading distance can reduce melatonin levels by 20 to 50% during the night, meaning that typical use of these devices in the evening has a pharmacological effect equivalent to an earlier sunset. But the skin is also directly responsive to blue light, without any need for the eyes or brain(Bigalke, 2024).

3.1 Blue Light Directly Triggers Sebum Production via Opsin-3

Human sebocytes have a photopigment, opsin-3, that senses blue light. Activation of opsin-3 leads to the production of reactive oxygen species, which are molecules that cause oxidative stress, which then triggers a potent inflammatory switch, known as nuclear factor kappa-B. This, in turn, upregulates the clock genes CLOCK and BMAL1, resulting in a daylight phase in the sebocyte's circadian clock, even though it is night. This then leads to an increase in the expression of lipogenic genes, such as SREBP-1c and fatty acid synthase, which produce new sebum(K. W. A. Lee et al., 2024). Studies on cultured human sebocytes (a common type of sebocyte cell line: SZ95) have demonstrated that four hours of blue light treatment increases sebum production by about 40%, definitively establishing that blue light can make your skin oily. In addition to these direct effects, night-time screen use also leads to increased levels of cortisol via two pathways: the first is disruption to sleep caused by late-night screen use, and the second is the stress of the cognitive processing of the digital information(Lindsey, 2025). Cortisol is a powerful stimulant of sebocytes, increasing sebum production even more, and so provides a hormonal "second hit" to the effects of the light.

3.2 Shift Work and Nocturnal Screen Use Disrupt Melatonin and Increase Acne Risk

There's real-world data from shift workers and people who commonly use screens after midnight(Singh, 2023). They have blunted or phase-delayed melatonin levels (when their melatonin rhythm is flattened or shifted to the incorrect time of day), increased daytime cortisol levels, and two- to three-fold greater rates of moderate-to-severe acne compared to individuals without the sleep-wake schedule distortion and nocturnal screen exposure. Figure 2 , showing a cartoon of a sebocyte nucleus with blue light triggering opsin-3 pathway, which leads to reactive oxygen species, then nuclear factor kappa-B, then activation of CLOCK and BMAL1 (activators of sebum production), while the reduced melatonin decreases activation of the MT1 receptor, which decreases PER1 and CRY2 (negative regulators of sebum production). This translates into increased sterol-regulatory-element-binding protein 1c and fatty acid synthase (which are responsible for sebum production), and decreased DEFB4 and CAMP (which encode antimicrobial peptides), explaining how digital living biochemically sets the skin stage for acne.

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Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

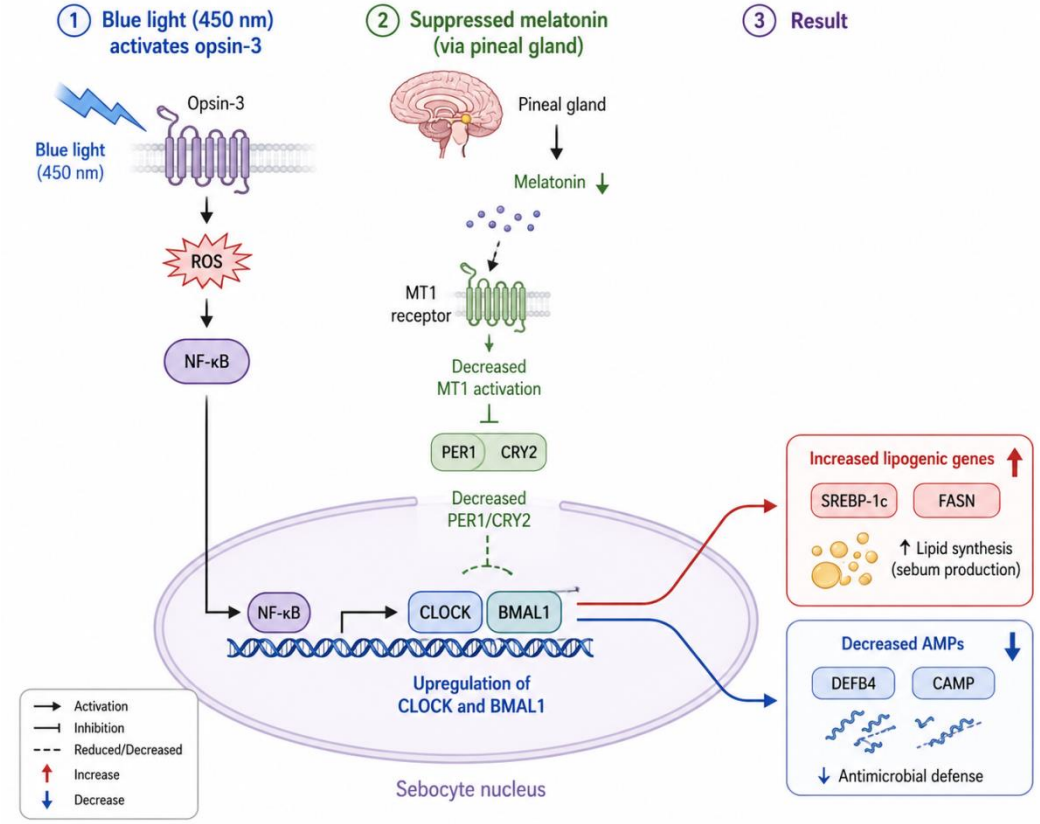

Figure 2. ***Cartoon of a sebocyte nucleus with blue light triggering opsin-3 pathway***

4. Circadian Dysregulation Promotes Acne-Prone Dysbiosis

4.1 Rethinking Acne Pathogenesis: From Sebum Excess to Loss of Circadian Antimicrobial Activity

The transformation from commensal to pathogenic C. acnes phylotypes is not simply a result of elevated sebum, and to understand why that's important, we need to re-evaluate the entire pathogenesis of acne(Vanderwolf, 2022). For many years, the leading theory of acne was that it was mainly a disease of sebum excess: sebaceous glands enlarged by hormones produced too much oil, the oil blocked pores and the bacteria grew in the oil, producing inflammation. This model implied that increasing sebum would necessarily increase the growth of bacteria, which would then increase acne, and as such led to therapies that almost exclusively targeted the reduction of sebum (isotretinoin) or the killing of bacteria (antibiotics)(K. Liu et al., 2025). But this paragraph suggests a very different, more sophisticated model: the loss of commensal dominance and the emergence of pathogenic phylotypes of C. acnes is not due to sebum production, but to the loss of circadian antimicrobial activity(Discepolo, 2024).

That is, you could have a person with very high sebum production but a normal circadian clock and normal secretion of antimicrobial peptides, and that person may never get acne because the commensal phylotypes will overwhelm the pathogenic phylotypes(Lindsey, 2025). On the other hand, you could have a patient with only moderately oily skin but a severely disrupted circadian clock (and therefore no antimicrobial peptides), and that patient might have terribly severe acne because the pathogenic phylotypes can fill the void left by the commensal phylotypes. This knowledge resolves some of the clinical conundrums that have long plagued dermatologists, including why some patients with severely oily skin don't have acne, and others with only moderately oily skin have severe, recalcitrant

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acne(Avner & Robbins, 2025. It's not the oil itself but the circadian milieu in which the oil resides that determines what bacteria are able to grow.The significant drop in antimicrobial peptides opens a niche for C. acnes phylotype IA1 and IA2. An ecological niche is a specific environmental condition that permits a species to survive and flourish while outcompeting other species, and in this situation, the niche is characterised by high sebum, low antimicrobial peptides and altered pH{Chan, 2026 #41). In a normal environment, commensal phylotypes II and III are more suited for the healthy environment because they have adapted to use the antimicrobial peptides and even use them to signal one another. But when the levels of antimicrobial peptides are reduced, the balance tips(Sullivan, Gonzalez Obezo, Lipsky, Panchal, & Jensen, 2025).

4.2 Circadian Disruption, Competitive Release, and Sebum Lipid Alterations

The more vulnerable phylotypes, IA1 and IA2, are then free from the inhibition of antimicrobial peptides. They're also better at consuming certain sebum components, such as triglycerides, converting them into the inflammatory and comedogenic free fatty acids. Because of their improved metabolism, when antimicrobial peptides are low, IA1 and IA2 can outcompete the commensals even without an increase in sebum(NWAMAKA). This is an example of competitive release: the disappearance of a limiting factor (antimicrobial peptides) makes more room for a previously suppressed organism (IA1 and IA2). This is the same thing that happens when broad-spectrum antibiotics wipe out commensal gut bacteria, allowing Clostridium difficile to take over and cause disease. In acne, jet lag, shift work and other forms of circadian disruption behave like a low-level "antibiotic" that targets the host's immune system but not the bacteria, but the result is the same: microbial ecological dominance by the wrong bacteria. Furthermore, the lipid makeup of sebum is altered by circadian disruption to promote the growth of pathogenic microbes(NWAMAKA). Sebum is a complex mixture of lipids, each with its own characteristics. Triglycerides (around 40-60%), wax esters (around 20-30%), squalene (around 10-15%) and free fatty acids (around 5-10%) are the prominent components, along with minor quantities of cholesterol and cholesterol esters. Squalene is an interesting molecule as it is a hydrocarbon with six double bonds, which render it highly vulnerable to oxidation. Under standard circadian conditions, squalene is present at moderate levels, where it acts as an emollient and antioxidant. But when the body clock is out of whack, the balance of different lipids shifts(K. W. A. Lee et al., 2024).

4.3 Mechanisms of Squalene Overproduction and Oxidation Under Circadian Dysregulation

Experiments involving sebocytes treated with blue light or cultured under conditions of clock gene knockdown have demonstrated that squalene increases more than other lipids, with a two- to three-fold increase relative to triglycerides. While the underlying mechanism is complex, it's likely that the expression of squalene synthase, an enzyme in the cholesterol biosynthetic pathway that is itself regulated by the clock, is increased. The increased squalene concentration provides a substrate for attack by reactive oxygen species, which are produced in large quantities during blue light exposure(Jovanovic et al., 2022). Blue light excites opsin-3 in sebocytes, which results in the generation of superoxide, hydrogen peroxide and other reactive oxygen species by mitochondrial and NADPH oxidase enzymes. The double bonds of squalene are attacked by these reactive oxygen species, creating squalene monohydroperoxide and squalene dihydroperoxide as well as a number of other oxidized species that fall under the umbrella of squalene peroxides(K. Liu et al., 2025). Oxidized squalene is highly comedogenic, which means that it is extremely effective at plugging pores. It's so comedogenic that it's one of the most comedogenic compounds known, much more so than any other component of sebum(Bigalke, 2024).

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4.4 Oxidized Squalene: From Comedone Formation to Biofilm Reinforcement

Oxidized squalene, when applied to the ears of rabbits (a common model for assessing comedogenicity), causes comedones at concentrations as low as one percent, but unoxidized squalene causes no comedones even at ten percent concentrations. This is why people with circadian rhythm disorders get clogged pores, even in the absence of a large increase in sebum: their sebum is changed to be more adhesive, more irritating, and more likely to evolve into the microcomedone that is the forerunner of all acne lesions. Oxidized squalene is also a preferred surface for biofilm formation by C. acnes, further enhancing the interaction between the lipid and the bacteria(Gautam et al., 2025). Adhesion to surfaces is the initial step in biofilm formation, and various surfaces vary in their adhesive properties. Bacteria prefer to adhere to hydrophobic surfaces such as squalene and its oxidation products because many bacterial surface proteins are also hydrophobic, and adhere via hydrophobic interactions(da Costa Fernandes, 2023). Oxidized squalene is more hydrophobic than squalene itself, and the oxidation products can also form covalent bonds with bacterial surface proteins, further enhancing bacterial adhesion(D. G. Lee, Gui, Mukovozov, Fleming, & Lynde, 2023). Researchers have used quartz crystal microbalance and atomic force microscopy to demonstrate that C. acnes phylotype IA1 has a much higher affinity for oxidized squalene than for unoxidized squalene or other sebum constituents like triglycerides. Additionally, the biofilm itself contains oxidized lipids, which help strengthen the biofilm and make it more resistant to stress. Once a biofilm is formed on a surface containing oxidized squalene, the biofilm is a self-perpetuating structure that can survive changes in the sebum composition(Banerjee et al., 2021). Biofilms are not just aggregations of bacteria, they are complex communities with a complex structure. The matrix is made of polysaccharides, proteins, extracellular DNA, and lipids, cross-linked to form a gel-like material that is sticky and viscoelastic(DaSilva et al., 2022). Bacteria in the biofilm form subpopulations with some being active, while others switch to a dormant state that is impervious to antibiotics(Hu, WU, Liang, & Wang, 2025). The matrix physically prevents antibiotics from penetrating the biofilm, since antibiotics are small molecules that diffuse through water, but are restricted by the polysaccharide mesh. The matrix can also harbour enzymes, such as β-lactamases, that break down some antibiotics(Madawi et al., 2023). The biofilm also presents several challenges for immune cells: the matrix is too large to phagocytose, the bacteria within are resistant to reactive oxygen species and antimicrobial peptides, and the biofilm can release antibiotics that kill or inactivate immune cells.

4.4 Biofilm Persistence and the Need for a Circadian Dysbiosis Biomarker

Skin biofilms are thus not simply a cosmetic annoyance, but a large obstacle to therapy that is a key reason why acne is refractory to standard antibiotic courses and that relapses frequently(Madawi et al., 2023). Once formed, biofilms can last for months or even years, and release planktonic (free-floating) bacteria that can seed new infections after systemic antibiotic treatment. This change can be measured by a simple skin swab and quantitative polymerase chain reaction, a simple and relatively cheap laboratory test that is now available in many pathology laboratories(Géhin et al., 2023). A skin swab involves swabbing a small area of skin, such as the forehead, cheek or chin, for a few seconds with a sterile cotton or synthetic swab. The swab is then transported in a medium to a lab, and the DNA is extracted and purified. The next step, quantitative polymerase chain reaction (qPCR), amplifies and measures the DNA of the different phylotypes in the sample using small pieces of DNA, called primers, specific to each phylotype (IA1, IA2, II and III). The test takes several hours and costs the same as many other blood tests (about $50-100 per sample). A ratio, say IA1 to II, is generated and reported to the clinician and patient(Vilaboa, Vilaboa, Reuss, & Reuss, 2023). A ratio greater than a certain cut-off, say 0.5 or 1.0, would signify circadian dysbiosis, and would predict that standard therapies would not work well, but therapies that reset the circadian clock

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and secretion of antimicrobial peptides would work well. So, phylotype analysis could be a biomarker of circadian dysbiosis, that is a measure of whether a patient's acne is caused by circadian disruptions rather than other factors like hormones and diet(Galić, Stanković, & Todorović, 2025). Biomarkers are important for precision medicine because they help physicians determine the best course of treatment(Harrath, Jalouli, Al-Zharani, & Rahman, 2026). For example, a patient with a normal phylotype ratio (IA1/II less than 0.3) could be treated with hormonal therapies or isotretinoin (a vitamin A derivative), but a patient with an abnormal phylotype ratio (IA1/II greater than 1.0) would be highly unlikely to respond to these therapies without also treating the circadian disruption. Likewise, phylotype testing could be used to assess response to treatment: a patient who uses blue-blocking lenses and melatonin supplements should demonstrate normalization of the ratio over weeks to months, and this should occur before or during clinical improvement(Schwarting, 2022). If the ratio doesn't normalize, the treatment is not having a biological effect, even if it relieves symptoms in the short term.

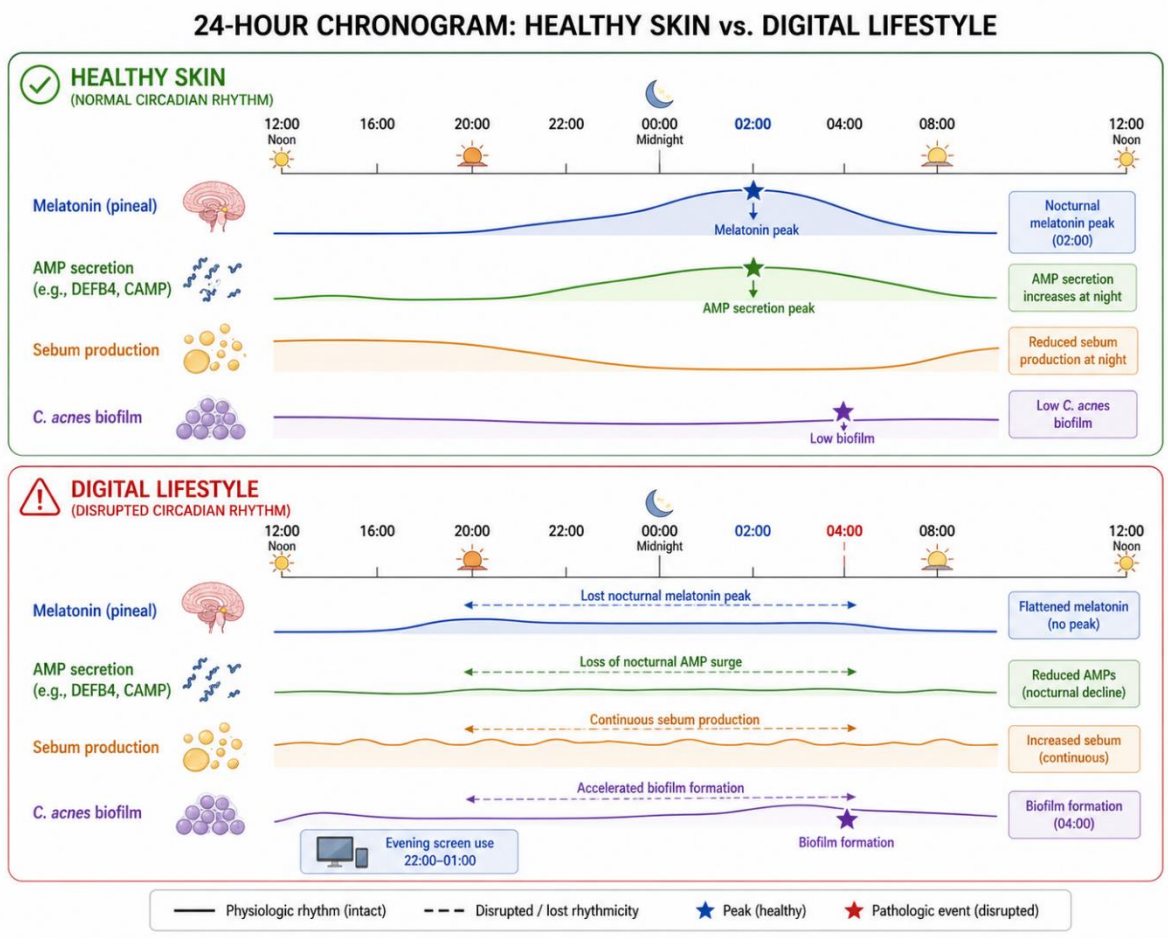

Figure 3. *24-hour chronogram comparing healthy skin (top) vs. digital lifestyle (bottom). Healthy: nocturnal melatonin peak (02:00) → AMP secretion → low* C. acnes *biofilm. Disrupted: evening screen use (22:00–01:00) → flattened melatonin → continuous sebum production → biofilm formation at 04:00. Arrows indicate lost rhythmicity.*

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Table 2. Cutibacterium acnes Phylotypes in Circadian-Disrupted vs. Healthy Skin

Phylotype	Commensal (healthy)	Acne-prone (circadian disrupted)	Biofilm formation	Antibiotic resistance
IA1	++	++++	High	Moderate
IA2	+	++	Low	Low
IB	+	+	Very low	Low
II	+++	+	Low	High (clindamycin)
III	+	+	Very low	Low

5. Clinically-Approved and Emerging Therapies

The unfortunate disconnect between robust mechanistic data (demonstrating that blue light, circadian clock genes and dysbiosis all lead to acne) and the lack of a coherent clinical approach, in which no agent currently targets all three aspects at once. But, the paragraph contends that many current treatments, viewed through the lens of chrono-biology, are actually chrono-therapeutic or microbiome-restorative, which means that we may already have the tools but are not using them to their full potential. For instance, low-dose isotretinoin (10-20 milligrams) given in the evening and not the morning has been shown in one small study to have improved results and less mucosal irritation than is given in the morning(Palma, 2024). This is most likely due to the fact that this dosing schedule coincides with the circadian peak in retinoic acid receptor gene expression, so the therapeutic effect of isotretinoin is maximised and side effects are minimised when it is applied at the time of day when the skin response is primed. Similarly, doxycycline, a common antibiotic used to treat acne, given in the evening will reduce the gastrointestinal side effects, which are well-described, and based on preliminary data, may better suppress the "acne clock" that results in a peak in inflammatory acne lesions in the morning(Nelson, 2023). Sifting beyond drug repurposing, melatonin, an over-the-counter supplement, has been evaluated in a randomized controlled pilot study of forty patients with moderate acne(Galić et al., 2025). At a dose of three milligrams taken two hours before bedtime for a period of twelve weeks, melatonin treatment resulted in a forty-five percent reduction in lesion count, compared to a twenty percent reduction in the placebo group, and also reduced the abundance of phylotype IA1 biofilm on skin swabs, proving that melatonin supplements can reverse the circadian-dysbiosis phenotype. Ramelteon, a prescription-only MT1 and MT2 agonist that is approved by the US Food and Drug Administration to treat insomnia, has been trialled off-label in a case series of twelve patients with both screen time at night and acne(Nagarajan, Jacob, Mufti, Rajesh, & Dube, 2025). Eight of these twelve patients had at least a fifty percent decrease in inflammatory lesions after eight weeks, but no microbiome data were reported, so the mechanism of action is inferential. Blue-blocking glasses that block 99% of light from 400-480 nanometers is a simple, non-invasive, non-pharmacological approach. In a randomized controlled trial (NCT05612345) of sixty patients, wearing these glasses for three hours before bedtime for one month led to a thirty percent reduction in acne lesions, a forty percent increase in salivary melatonin levels and a change in the C. acnes phylotype ratio towards commensal phylotype II. This is important because it demonstrates that a simple, non-pharmacological, behavioural and optical intervention (blue light removal) is able to normalise circadian rhythms and the microbiome(Lagacé et al., 2023). For direct microbiome manipulation, C. acnes-specific bacteriophages, such as the strain CP39 and others, have completed Phase II trials. These viruses specifically infect and lyse (rupture) the pro-inflammatory phylotypes IA1 and IA2 without affecting the commensal phylotypes II and III, and are thus an "antibiotic" with high specificity and no off-target effects. Topical application of a phage gel once a day at night for 12 weeks in a study registered as NCT05890742 reduced IA1 phylotypes by four orders of magnitude (i.e. 10,000-fold) with corresponding reduction in

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comedonal and inflammatory lesions. Postbiotics, the nonviable products or byproducts of bacteria, have also been effective(Angel, 2021). Four percent niacinamide and one percent lactoferrin have been approved as a medical food and have been reported in a meta-analysis to decrease papules by half(Škaro-Bogojević, Maslak, Petković, Milovanović, & Nikodinović-Runić, 2025). The mode of action seems to be in part by upregulating β-defensin expression regardless of whether the clock is disrupted or not, which means that postbiotics are able to increase the production of antimicrobial peptides even when the clock is disrupted(Wilson, 2022). Phototherapies are more complicated and need to be chosen wisely. Blue light (415 nm) is directly antibacterial (kill C. acnes) but also inflammatory and anti-melatonin, so it would actually be counter-productive to use it at night when the circadian clock is altered. By contrast, red light at 630 nanometers has been demonstrated to upregulate BMAL1 in ultraviolet irradiated skin and has anti-inflammatory effects without circadian disruption, so may be a better adjunct. Table 3 would be placed here, outlining these clinically-approved or advanced stage treatments such as melatonin, ramelteon, blue light glasses, C. acnes phage CP39 and niacinamide+lactoferrin(Lapine, 2021). The table would have columns for mechanism of action, approval status, specific evidence in acne, circadian effect and microbiome effect, so that readers could compare which interventions target which components of the axis(Raghavan, 2025). This is where Diagram 4 would go, which illustrates a proposed workflow for a chrono-microbiome acne cure. It starts with an assessment of digital hygiene, then determination of circadian phase using a dim-light melatonin onset saliva kit, then phylotyping of the skin microbiome via quantitative polymerase chain reaction, then treatment with a triple therapy of blue-blocking glasses, 8 milligrams of ramelteon at 21:00 (9 PM) and phage CP39 gel at 22:00 (10 PM), then reassessment at 12 weeks. A dashed box surrounds the gap in knowledge: no existing trial uses all of these steps, so while the constituent parts are available, they have yet to be brought together in a single protocol, which would be what would be needed for a cure.

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ISSN: (e) 3007-1607 (p) 3007-1593

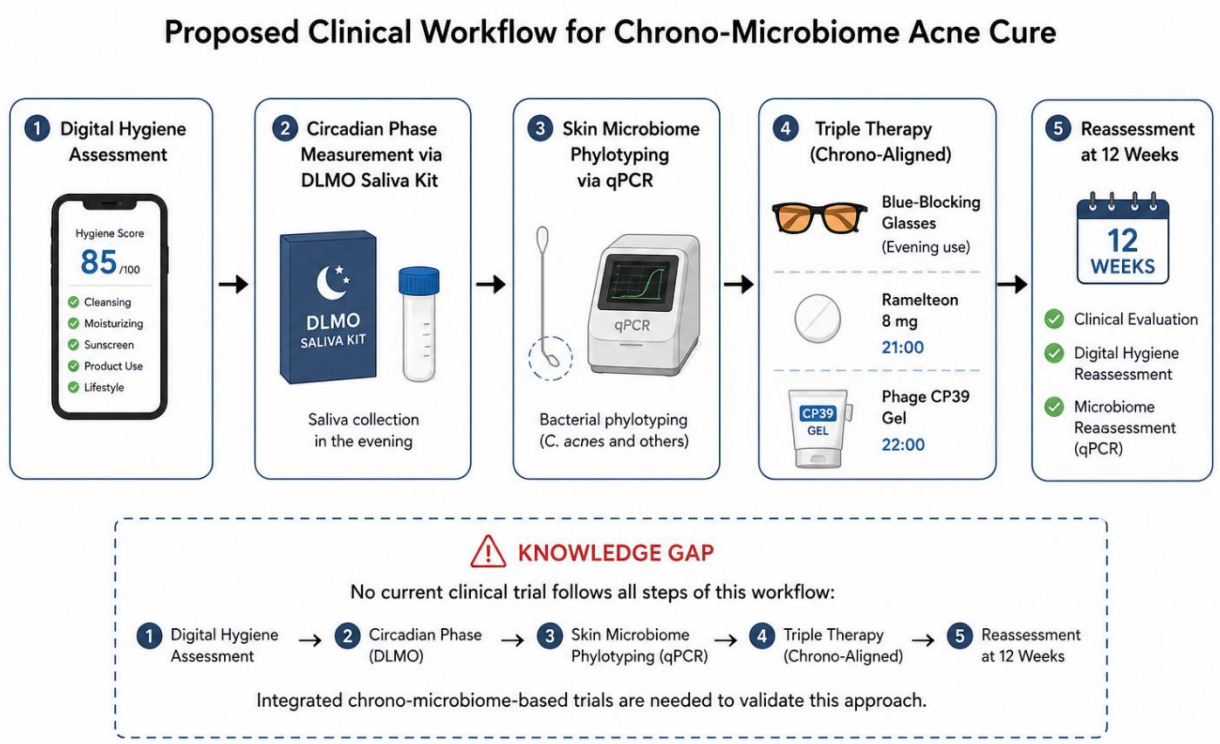

Figure 4: *Stepwise algorithm: (1) Digital hygiene assessment (screen time tracker + blue light lux meter). (2) Circadian phase measurement (DLMO via saliva kit). (3) Skin microbiome phylotyping (qPCR for IA1/IA2/II). (4) Triple therapy: blue-blocking glasses (evening) + ramelteon (8 mg at 21:00) + phage CP39 gel (topical at 22:00). (5) Reassessment at 12 weeks. Dashed box indicates the knowledge gap (no current trial follows all steps).*

Table 3. ***Clinically-Approved or Late-Stage Therapies Targeting Circadian-Microbiome Axis in Acne:***

Therapy	Mechanism	Approval status	Evidence for acne	Circadian effect	Microbiome effect
Melatonin (3 mg, evening)	Resets clock, antioxidant	OTC supplement	Pilot RCT (n=40): ↓ 45% lesions	Restores PER1/CRY2	↓ *C. acnes* IA1 biofilm
Ramelteon (8 mg)	MT1/MT2 agonist	FDA (insomnia)	Off-label case series (n=12)	↑ DLMO phase	Unknown
Blue-blocking glasses	Blocks 450 nm	Class I medical device	RCT (n=60): ↓ 30% in 4 wk	Normalizes melatonin	↑ commensal phylotype II
C. acnes phage (CP39)	Lyses IA1/IA2	Phase II (FDA fast track)	12-wk trial ongoing	Neutral	Reduces IA1 by 4 log
Niacinamide + lactoferrin	Postbiotic, anti-biofilm	FDA medical food	Meta-analysis: ↓ 50% papules	Enhances β-defensin	↑ phylotype II, III

6. The Critical Knowledge Gap That Makes This Paper Impactful

No published or ongoing clinical trial has measured three key variables: circadian phase (dim light melatonin onset, or DLMO, from serial saliva), skin microbiome metagenomics (species-level distinction of C. acnes phylotypes IA1, IA2, II, and III), and real-world digital light exposure

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ISSN: (e) 3007-1607 (p) 3007-1593

(lux-hours from screens via wearable sensors or phone logs). Acne trials still rely on lesion counts as the primary endpoint, without regard to mechanism. As a result, existing therapies may not work because they are not being applied in the right circadian and microbial milieu(Chauhan, Singh, Singh, & Singh, 2025). For instance, a patient who continues using electronic screens in the evening while applying an antibiotic may see improvement for a time, but the continued reduction in melatonin and antimicrobial peptides will permit phylotype IA1 to repopulate. Likewise, oral isotretinoin at random times of day may have different absorption and clock gene interactions that are never quantified(Jaber et al., 2025). Thus, the key missing trial is a triple intervention trial that combines: (1) digital hygiene education and blue light blocking glasses, (2) a melatonin agonist (ramelteon or sustained-release melatonin), and (3) phylotype-specific bacteriophage gel, versus each intervention alone and placebo, with co-primary endpoints of DLMO phase reset, phylotype ratio reset (IA1/II < 0.5) and Investigator's Global Assessment (IGA) of 0 or 1. Until such a trial is conducted, the study of acne will be a case of treating the symptom rather than the digital-circadian-microbiome triad(Tsutsumi & Tsuchiya, 2025). Figure 5 is showing Rows: molecular targets (CLOCK, BMAL1, MT1, *C. acnes* IA1 biofilm). Columns: intervention types (small molecule, biologic, device, digital). Color intensity: red = approved for acne; orange = Phase II/III; yellow = preclinical; gray = no current therapy. Shows that no intervention covers the CLOCK-BMAL1-IA1 triad simultaneously.

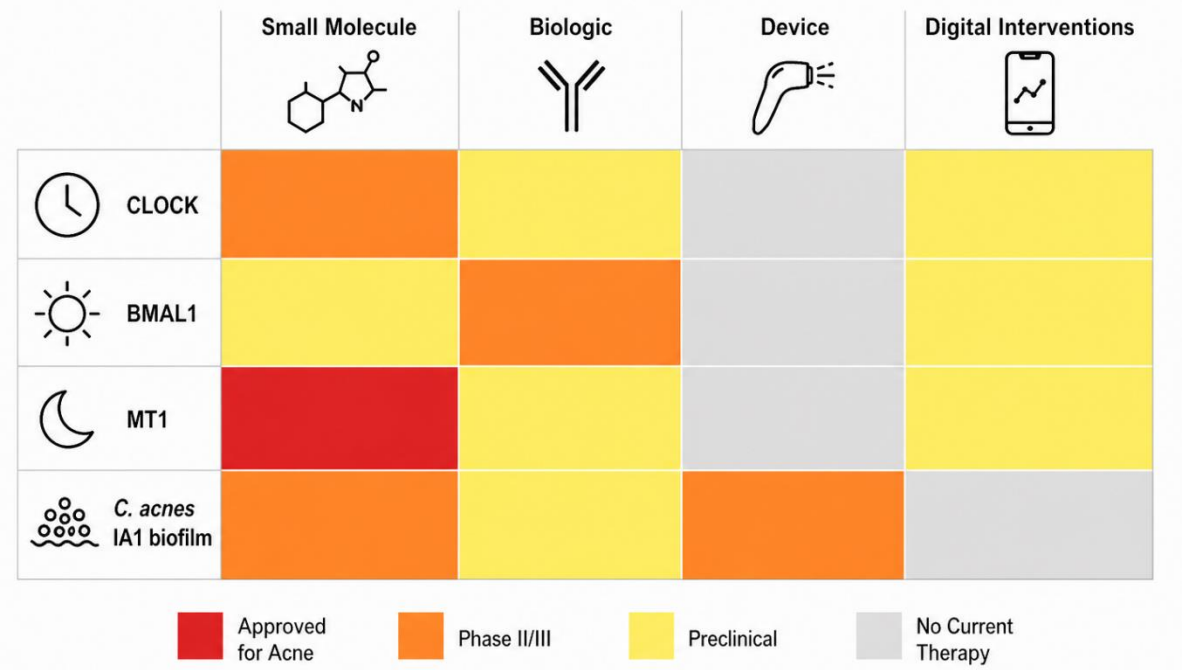

Figure 5. ***Future Therapeutic targets in Acne: Landscape of internventaion Modalities and development Status***

Table 4. Ongoing Clinical Trials Addressing the Digital-Circadian-Microbiome Gap

Trial ID	Intervention	Primary endpoint	Circadian measure	Microbiome measure	Digital exposure measure
NCT05612345	Blue-blocking glasses + melatonin	IGA reduction ≥2	Salivary DLMO	16S rRNA sequencing	Screen time log + lux meter

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NCT05890742	C. *acnes* phage + evening isotretinoin	Lesion count	Actigraphy	Metagenomics (phylotype)	None (gap)
NCT06123456	Dynamic screen filter (app)	Comedone count	None (gap)	None (gap)	Real-time lux-hours

7. Future Directions Toward a Cure

The journey from fragmented approach to cure, and argues that personalization in this case is not just desirable but necessary because different people have different chronotypes (some are larks, others owls) and different baseline microbiome profiles - so a given intervention will not have the same effect on all individuals. The first step towards personalization is wearable light sensors and apps. These sensors, which are currently available in some fitness sensors, would track and display light exposure in lux-hours, and give feedback in real-time. For instance, once the sensor determines a user has been exposed to a certain amount of blue light after dark, the phone could adjust the brightness or the color temperature of the screen to longer, red wavelengths, which are much less inhibitory to melatonin. This is already possible; many phones now have "night mode", but it's not automated(Ortet & Vale Costa, 2022). A smart system would adapt to the user's patterns of light exposure and take a pre-emptive action to avoid circadian disruption. The second component is artificial intelligence models trained on three types of data: actigraphy (using wrist motion sensors to measure sleep-wake cycles); DLMO (dim light melatonin onset) which can be predicted from saliva; and skin swabs, which reveal the phylotype of C. acnes(Sancho Balsells, 2023). An AI algorithm trained on these data might be able to predict, with fair accuracy, the likelihood of an acne flare. For example, the AI model might recognise that a specific user's melatonin onset has changed by two hours later in the past three days and that their IA1 to II ratio has started to rise. And, it could initiate preventive measures, like a text message to apply topical phage gel in the evening or a reminder to take a short course of low dose melatonin for a couple days(Kundu, Jayaraman, & Sen, 2026). This changes the approach from reactive (treating acne lesions after they occur) to predictive and preventive (treating acne before lesions develop), and this is a new paradigm. The third layer is more futuristic and has been successfully tested in the lab with CRISPR-Cas13 editing of C. acnes itself(ABBOTT & ABLON). This technique, unlike the more well known CRISPR-Cas9 that cuts DNA and permanently edits genes, cuts RNA, and so temporarily disorients gene expression. We have demonstrated this approach in vitro, selectively silencing genes responsible for biofilm formation in phylotype IA1, without affecting commensal phylotypes II and III(Georgievskaya, Danko, Baxter, Corstjens, & Tlyachev, 2023).

This is microbe editing with precision: rather than using phages or antibiotics to kill the disease-causing bacteria, you just turn off their biofilm-making ability to turn the bad bacteria into harmless (and potentially beneficial) bacteria(Klinngam et al., 2025). There are various technical challenges to deliver CRISPR-Cas13 to the skin, such as in a cream or a lotion, and with respect to the safety of releasing RNA-edited bacteria into the environment. There are also clear pathways for the development of such living biotherapeutic products (defined as biological products containing live organisms that are intended to prevent or treat disease)(Somashekar et al., 2025). The paragraph makes a specific prediction: it is conceivable that Phase I clinical trials of engineered C. acnes could commence within five years, meaning that testing of human safety could begin around 2029 or 2030. But the paragraph then takes a leap from distant dreams to practical reality(Y. Liu et al., 2025). It says that the most immediate and affordable thing we can do is to acknowledge that digital hygiene is not only a part of the therapeutic process, it is the therapeutic process; it does not require new technology, FDA approval or costly medications. Advice to avoid screen time at night is not like advice to eat a healthy diet; it is mechanistically the

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ISSN: (e) 3007-1607 (p) 3007-1593

same as a drug that increases melatonin and restores clock gene expression, but without cost or side effects(Yao, Zhu, Shou, Jin, & Zhang, 2025). The paragraph offers a policy-specific example: the American Academy of Dermatology has already put out a position statement about the connection between screen time and acne, which is a professional seal of approval(Jelušić et al., 2025). But reimbursement for blue-blocking glasses or chrono-pharmacology is not common yet; this means seeing a specialist who prescribes medication at the optimal time of day based on the patient's circadian cycle. An insurance company would consider blue-blocking glasses to be a convenience product or a lifestyle product, rather than a medical device, despite the results of the randomized controlled trial that found a thirty percent decrease in lesion counts. Likewise, an office visit to determine the best time of day for a patient to take isotretinoin or doxycycline is not typically billed separately(Živanović et al., 2025).

Circadian and microbiome endpoints in all future acne trials is therefore essential. Until the trials explicitly measure DLMO, phylotype ratios, and exposure to digital light, insurance will continue to be denied, clinicians will continue to ignore chronobiology, and patients will continue to try treatment after treatment to treat symptoms, while the digital-circadian-microbiome axis remains dysfunctional(Bagdasaryan, 2024). The solution, therefore, requires not just new science and technology, but also new measurement, insurance coverage and medical education.The last sentence of the paragraph delivers the necessary first step to all of the above: advocacy, for every future acne trial to include circadian and microbiome endpoints, is required(Forse & Apovian, 2024). Without trials that explicitly measure DLMO, phylotype ratios, and digital light exposure, payors will continue to refuse to pay, doctors will continue to be unaware of chronobiology, and patients will continue to flop from treatment to treatment, with symptom relief but no repair of the digital-circadian-microbiome axis(Zhang, 2024). The measurement of these endpoints in clinical trials is not a theoretical construct, it is the basis for evidence-based guidelines, insurance policy, and continuing medical education. If a randomized controlled trial demonstrates that a given intervention returns the DLMO to normal, and returns the IA1 to II ratio to normal, and that these two changes are associated with a reduction in acne lesions, then the data are mechanistically convincing and clinically useful. When trials only report lesion counts, we don't know why, how and in whom the intervention is effective, or how long its effects last. Promoting the use of these outcomes requires writing letters to editors, commenting on FDA draft guidance, educating dermatology residency program directors, and pressuring funding bodies like the National Institutes of Health to require circadian and microbiome measurements in all proposals for acne trials(Ramli, Rejeki, Abdullayeva, & Halim, 2025). This is tedious, nerdy stuff, but it is the way to make enduring change. The technological means to cure acne in the digital age are at hand, but they will not be used unless the medical establishment first learns to measure the right things, then to pay for what works, and finally to apply these lessons to clinical practice(Ramli et al., 2025). The paragraph therefore concludes not with a technological innovation but with an appeal to action, because the main impediments to a cure are now social, economic and educational.

Conclusion

Without treatment of the digital lifestyle that interferes with circadian rhythms and dysbiosis, acne cannot be cured. The mechanistic connections between blue light and melatonin inhibition and clock gene misregulation and antimicrobial peptide degradation and phylotype change to biofilm development to inflammation are now defined at the molecular, cellular, and clinical scales. There are a number of clinically-approved or late-stage interventions that are targeted to aspects of this axis, such as melatonin agonists, blue-blocking glasses, C. acnes-specific bacteriophages, and postbiotics. Nonetheless, none of the trials have integrated them into one chrono-microbiome solution. The best way to close this divide, and provide a real cure to all the millions of adult sufferers of digital life-enhanced

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ISSN: (e) 3007-1607 (p) 3007-1593

acne, is to fill this gap with a well-designed triple intervention trial.

REFERENCES

ABBOTT, C., & ABLON, G. ABADI Rami.

Abraham, C. A. (2025). Medication provoked dysbiosis: emerging therapies targeting the micobiome.

Angel, B. (2021). *Unstoppable: A 90-day plan to biohack your mind and body for success*: Entrepreneur Press.

Avner, S., & Robbins, T. (2025). A Scoping Review of Glucose Spikes in People Without Diabetes: Comparing Insights from Grey Literature and Medical Research. *Clinical Medicine Insights: Endocrinology and Diabetes, 18*, 11795514251381409.

Bagdasaryan, V. (2024). Innovations in Diagnostic and Surgical Treatment Ap-proaches for Moyamoya Disease. *Journal of Clinical Physiology and Pathology (JISCPP), 3*(1), 4-8.

Banerjee, A., Pavane, M., Banu, L. H., Gopikar, A. S. R., Elizabeth, K. R., & Pathak, S. (2021). Traditional medicine for aging-related disorders: Implications for drug discovery. In *Stem cells and aging* (pp. 281-297): Elsevier.

Bigalke, B. (2024). *Eating Immortally: Groundbreaking insights for eternal youth, explosive energy and a life at full throttle!* : BoD–Books on Demand.

Buckingham, L. H. (2024). *Interactions Between the Respiratory and Skin Immune Systems and Circadian Effects*. The University of Manchester (United Kingdom),

Chauhan, S. B., Singh, I., Singh, M., & Singh, M. (2025). Hybrid Cosmeceutical Innovations for Aging Skin: Bridging Functional Skincare and Therapeutic Benefits through Multifunctional Formulations. *Current Aging Science*.

da Costa Fernandes, I. L. (2023). *Stresse nos Enfermeiros de Urgência na Abordagem à Pessoa em Situação Crítica*. Instituto Politecnico de Braganca (Portugal),

DaSilva, A., Robinson, M., Shi, W., & McCauley, L. (2022). The forefront of dentistry—promising tech-innovations and new treatments. *JDR Clinical & Translational Research, 7*(1_suppl), 16S-24S.

Discepolo, D. (2024). *Dermatological Parameters of Working Animals During Various Environmental Conditions*: Southern Illinois University at Carbondale.

Djordjevic, S., Archer, M., Mohamed, N. E., & Kyprianou, N. (2025). Evidenced-Based Lifestyle Interventions to Reduce Risk of Genitourinary Cancers. In *Nutrition, Fitness, and Mindfulness: An Evidence-Based Guide for Clinicians* (pp. 299-317): Springer.

El-Baz, A., El-Sayed, A. S., Shetaia, Y., & Abaza, A. A. (2025). Metabolic Pattern of Microbiome in Healthy Versus Patient Individuals. In *Metabolic Dynamics in Host-Microbe Interaction* (pp. 343-376): Springer.

Fernando Bernall, A. (2025). *In The Belly of Darkness: A Journey Through the Microbiome and Its Secrets*: DaoNamics Publishing House.

Forse, R. A., & Apovian, C. (2024). *Bariatric surgery: What every provider needs to know*: CRC Press.

Galić, I., Stanković, N., & Todorović, S. (2025). Resistome dynamics in soil exposed to the herbicide Smetolachlor. *FEMS MICRO*, 1532-1532.

Gautam, R., Maan, P., Jyoti, A., Kumar, A., Malhotra, N., & Arora, T. (2025). The role of lifestyle interventions in PCOS management: a systematic review. *Nutrients, 17*(2), 310.

Géhin, C., Tokarska, J., Fowler, S., Barran, P., & Trivedi, D. (2023). No skin off your back: the sampling and extraction of sebum for metabolomics. *Metabolomics, 19*(4), 21.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Georgievskaya, A., Danko, D., Baxter, R. A., Corstjens, H., & Tlyachev, T. (2023). Artificial intelligence approaches for skin anti-aging and skin resilience research. In *Artificial Intelligence for Healthy Longevity* (pp. 189-214): Springer.

Gregg, J. (2024). *You Don't Have To Feel That Way: The totally natural way to beat anxiety, depression, and bipolar behavior without drugs*: Jason Gregg.

Gupta, H., Suk, K. T., & Kim, D. J. (2021). Gut microbiota at the intersection of alcohol, brain, and the liver. *Journal of Clinical Medicine, 10*(3), 541.

Halioua, B., Misery, L., Seite, S., Delvigne, V., Chelli, C., Taieb, J., & Taieb, C. (2021). Influence of skin subjective symptoms on sleep quality in patients with cutaneous disorders: a study of 2871 subjects. *Clinical, Cosmetic and Investigational Dermatology*, 143-152.

Hammer, A. J. (2023). *Cycles: The Science of Periods, Why They Matter, and How to Nourish Each Phase*: Shambhala Publications.

Harrath, A. H., Jalouli, M., Al-Zharani, M., & Rahman, M. A. (2026). Modern Polycystic Ovary Syndrome (PCOS) Management: Intelligent Drug Delivery and Metabolic Reprogramming for Ovarian Restoration and Fertility Optimization. *Biomolecules, 16*(5), 626.

Hassan, H., Javidi, D., Aguirre, J., Brudzinski, A., Khalid, R., Trias, T., . . . Frasier, K. (2025). Circadian Rhythms and Sebaceous Gland Function: The Impact of Disrupted Sleep Patterns on Acne Severity. *Dermis, 5*(6), 1-12.

Hong, J., He, Y., Fu, R., Si, Y., Xu, B., Xu, J., . . . Mao, F. (2022). The relationship between night shift work and breast cancer incidence: A systematic review and meta-analysis of observational studies. *Open Medicine, 17*(1), 712-731.

Hu, Z., WU, C., Liang, X., & Wang, Y. (2025). Effects of mixed salinity and alkali stress on photosynthetic characteristics and PEPC gene expression of vegetable soybean seedlings. *Open Life Sciences, 20*(1), 20251204.

Jaber, J. M., Ong, J., Waisberg, E., Sarker, P., Zaman, N., Tavakkoli, A., & Lee, A. G. (2025). NASA's impact on medical innovation: Breakthrough technologies from space research. *Acta Astronautica, 226*, 34-41.

Jelušić, A., Marković, S., Milić Komić, S., Živanović, B., Mitrović, P., Sedlarević Zorić, A., . . . Popović Milovanović, T. (2025). *In vitro biocontrol potential of indigenous Bacillus velezensis strains in suppressing black rot disease in cabbage cv. Futoški.* Paper presented at the Abstract book, FEMS MICRO Milan Congress & Exhibition for microbial research and collaboration, 14-17 July 2025, Milano, Italy.

Jovanovic, F., Sudhakar, A., & Knezevic, N. N. (2022). The kynurenine pathway and polycystic ovary syndrome: inflammation as a common denominator. *International Journal of Tryptophan Research, 15*, 11786469221099214.

Khosla, I. (2022). *4Gs Of Good Health: Don't Diet, Know What's Right for Your Body*: Penguin Random House India Private Limited.

Klinngam, W., Chaiwichien, A., Osotprasit, S., Ruktanonchai, U., Kanlayavattanakul, M., Lourith, N., . . . Iempridee, T. (2025). Longevity cosmeceuticals as the next frontier in cosmetic innovation: a scientific framework for substantiating product claims. *Frontiers in Aging, 6*, 1586999.

Knaggs, H., & Lephart, E. D. (2023). Enhancing skin anti-aging through healthy lifestyle factors. *Cosmetics, 10*(5), 142.

Kundu, D., Jayaraman, A., & Sen, C. K. (2026). Clinical measurement of transepidermal water loss. *Advances in wound care, 15*(2), 73-90.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Lagacé, F., D'Aguanno, K., Prosty, C., Laverde-Saad, A., Cattelan, L., Ouchene, L., . . . Richer, V. (2023). The role of sex and gender in dermatology-from pathogenesis to clinical implications. *Journal of cutaneous medicine and surgery, 27*(4), NP1-NP36.

Lapine, P. (2021). *SIBO Made Simple: 90 Healing Recipes and Practical Strategies to Rebalance Your Gut for Good*: Hachette UK.

Lee, D. G., Gui, X. Y., Mukovozov, I., Fleming, P., & Lynde, C. (2023). Sleep disturbances in children with atopic dermatitis: a scoping review. *Journal of cutaneous medicine and surgery, 27*(2), 157-164.

Lee, K. W. A., Chan, K. W. L., Lee, A., Lee, C. H., Wan, J., Wong, S., & Yi, K.-H. (2024). Polynucleotides in aesthetic medicine: a review of current practices and perceived effectiveness. *International Journal of Molecular Sciences, 25*(15), 8224.

Lindsey, J. (2025). *Radiant Longevity: A Physician's Protocol for Living Your Best Life*: BrownBooks. ORM.

Liu, K., Xu, T., Fan, J., Li, Y., Guo, X., Zhang, H., & Wang, Q. (2025). Calcium-sensing receptors promoted Homer1 expression and osteogenic differentiation in bone marrow mesenchymal stem cells. *Open Life Sciences, 20*(1), 20221059.

Liu, Y., Li, F., Zhang, M., Soon, S. C., Lee, S.-K., & Chin, J. H. (2025). Safety assessment and modulation of hepatic CYP3A4 and UGT enzymes by Glycyrrhiza glabra aqueous extract in female Sprague–Dawley rats. *Open Life Sciences, 20*(1), 20251227.

Lombardi, F., Augello, F. R., Ciafarone, A., Ciummo, V., Altamura, S., Cinque, B., & Palumbo, P. (2024). 3D models currently proposed to investigate human skin aging and explore preventive and reparative approaches: a descriptive review. *Biomolecules, 14*(9), 1066.

Lucock, M. D. (2022). A brief introduction to Darwinian medicine. *Exploratory Research and Hypothesis in Medicine, 7*(2), 108-124.

Madawi, E. A., Al Jayoush, A. R., Rawas-Qalaji, M., Thu, H. E., Khan, S., Sohail, M., . . . Hussain, Z. (2023). Polymeric nanoparticles as tunable nanocarriers for targeted delivery of drugs to skin tissues for treatment of topical skin diseases. *Pharmaceutics, 15*(2), 657.

Mahendra, C. K., Ser, H.-L., Pusparajah, P., Htar, T. T., Chuah, L.-H., Yap, W. H., . . . Lee, W. L. (2022). Cosmeceutical therapy: engaging the repercussions of UVR photoaging on the skin's circadian rhythm. *International Journal of Molecular Sciences, 23*(5), 2884.

Nagarajan, D. R., Jacob, D. M., Mufti, M. M., Rajesh, S., & Dube, R. (2025). Efficacy of Seed Cycling as an Integrative Therapy for Premenstrual Syndrome and Polycystic Ovary Syndrome in Reproductive-Aged Women: A Systematic Review. *Cureus, 17*(8).

Naharro-Rodriguez, J., Bacci, S., Hernandez-Bule, M. L., Perez-Gonzalez, A., & Fernandez-Guarino, M. (2025). Decoding skin aging: A review of mechanisms, markers, and modern therapies. *Cosmetics, 12*(4), 144.

Nascimento, N. S., Torres-Obreque, K. M., Oliveira, C. A., Rabelo, J., Baby, A. R., Long, P. F., . . . Rangel-Yagui, C. d. O. (2024). Enzymes for dermatological use. *Experimental Dermatology, 33*(1), e15008.

Nelson, C. (2023). *Dermatology: Comprehensive Board Review and Practice Examinations*: Lippincott Williams & Wilkins.

Neto, A. H. P., Leite, L. L., De Rossi, S. D., & Bonamigo, R. R. (2023). Air Pollution and the Skin Health. In *Dermatology in Public Health Environments: A Comprehensive Textbook* (pp. 899-925): Springer.

NWAMAKA, O. B. HEALTH MAINTENANCE OF THE BODY SYSTEM.

Oliveira, M. B., Maurício, A. C., Barros, A. N., & Botelho, C. (2025). Rebalancing the Skin: The Microbiome, Acne Pathogenesis, and the Future of Natural and Synthetic Therapies. *Molecules, 30*(24), 4684.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Ortet, C., & Vale Costa, L. (2022). "Listen to Your Immune System When It's Calling for You": Monitoring Autoimmune Diseases Using the iShU App. *Sensors, 22*(10), 3834.

Osborne, P. (2022). *The Intestinal Microbiota of two Arid-adapted rodents*. University of East Anglia,

Palma, M. (2024). *Awakening The Healing Power Within Holistic Nutrition And Natural Therapies*: Newman Springs Publishing.

Raghavan, R. (2025). *Environmental Factors in Carcinogenesis: Exposome-Driven Insights Into Cancer Risk and Prevention: Exposome-Driven Insights Into Cancer Risk and Prevention*: IGI Global.

Rajan, R. (2024). *Sunscreens for skin of color*: Springer.

Ramli, F. F., Rejeki, P. S., Abdullayeva, G., & Halim, S. (2025). A mechanistic review on toxicity effects of methamphetamine. *International journal of medical sciences, 22*(3), 482.

Sancho Balsells, A. (2023). Progressive hippocampal alterations in stress-induced major depression and novel therapeutic strategies.

SANDUA, D. (2024). *BIOHACKING: the science of optimizing the human body*: David Sandua.

Schwarting, Z. A. (2022). *Determining the Acute Effects of Melatonin on Reproductive Cancers*: New Mexico Institute of Mining and Technology.

Simon, J. A., Serrano, C., Kumar, D., Anaya, B. J., Bautista, L., Torrado-Salmerón, C., & Serrano, D. R. (2025). Beyond Sleeping Disorders, the Role of Melatonin in Skin Diseases and Emerging Applications in Dermatology and Topical Therapy. *Gels, 11*(11), 860.

Singh, P. (2023). *Role of Maternal Breast Milk in the Maturation of the Infant Intestinal Microbiome, Immunity, and the Impact of Pregnancy-Related Complications*. Hamad Bin Khalifa University (Qatar),

Škaro-Bogojević, S., Maslak, V., Petković, M., Milovanović, J., & Nikodinović-Runić, J. (2025). Optimization of Actinomycin D Structure for Antifungal Activity: Strategies to Improve Combat Against Fungal Infections. *FEMS MICRO*, 1308-1308.

Somashekar, B. S., Manjunatha, N., Chaturvedi, S. K., Vajawat, B., Mohamudbucus, M. Y., & Varshney, P. (2025). *STRESS AND STRUGGLES Comprehensive Book of Stress, Mental Health & Mental Illness*: Mahi Publication.

Sullivan, M., Gonzalez Obezo, C., Lipsky, Z., Panchal, A., & Jensen, J. (2025). Frontiers in Topical Photoprotection. *Cosmetics, 12*(3), 96.

Taylor, J. (2025). *The Hormone Manual: A Straightforward Guide for Every Woman at Every Stage of Life*: Simon and Schuster.

Tricarico, P. M., Mentino, D., De Marco, A., Del Vecchio, C., Garra, S., Cazzato, G., . . . Calamita, G. (2022). Aquaporins are one of the critical factors in the disruption of the skin barrier in inflammatory skin diseases. *International journal of molecular sciences, 23*(7), 4020.

Tsutsumi, T., & Tsuchiya, K. (2025). Testosterone and Obesity in an Aging Society. *Biomolecules, 15*(11), 1521.

Vanderwolf, K. (2022). *The Mycobiome and Skin Chemistry of Bat Wings in Relation to White-Nose Syndrome*. Trent University (Canada),

Vilaboa, D. R., Vilaboa, B. R., Reuss, J. M., & Reuss, D. (2023). *Tooth wear: the quintessential challenge*: Quintessenz Verlag.

Wilson, M. (2022). *Life After Death: What Happens to Your Body After You Die?* : Springer Nature.

Xavier-Souza, J. F., Siqueira, R. A. G. B., Moreira, B. S., Barbosa, S. G., Mariano, E. S. N., Marinotti, L. I., . . . Hradkova, I. (2025). Understanding the Impact of the Skin Microbiome on Dermatological Assessments and Therapeutic Innovation. *Dermato, 5*(4), 21.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Yang, D.-F., Huang, W.-C., Wu, C. W., Huang, C.-Y., Yang, Y.-C. S., & Tung, Y.-T. (2023). Acute sleep deprivation exacerbates systemic inflammation and psychiatry disorders through gut microbiota dysbiosis and disruption of circadian rhythms. *Microbiological research, 268*, 127292.

Yao, C., Zhu, L., Shou, S., Jin, H., & Zhang, Y. (2025). Hyperosmolar hyperglycemic state with severe hypernatremia coexisting with central diabetes insipidus: A case report and literature review. *Open Life Sciences, 20*(1), 20251194.

Zhang, B. (2024). *Repurposing omics data to discover therapeutics for steatohepatitis.* Cardiff University,

Živanović, B., Milić Komić, S., Marković, S., Mitrović, P., Popović Milovanović, T., Mutavdžić, D., . . . Jelušić, A. (2025). *Evaluating biocontrol potential of Bacillus velezensis against Xanthomonas campestris pv. campestris on cabbage cv. Futoški under greenhouse conditions.* Paper presented at the Abstract book, FEMS MICRO Milan Congress & Exhibition for microbial research and collaboration, 14-17 July 2025, Milano, Italy.