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Chronocosmetics: Molecular Clock–Guided Design of Phase-Specific Topical Therapeutics

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Abstract

The skin exhibits robust circadian rhythms regulating DNA repair, barrier homeostasis, cellular turnover, antioxidant defense, and sebum secretion. These day/night-dependent processes suggest that topical compound efficacy depends not only on concentration and properties but also on application timing. Chrono-cosmetics represent next-generation cosmeceutical technology, synchronizing dermatological actives with the skin's biological clock.Molecular clock factors (BMAL1, CLOCK, PER, CRY) coordinate regulation, while extrinsic factors (light, temperature, topicals) modulate peripheral clock gene expression. Disrupted circadian regulation causes photoaging, barrier dysfunction, inflammation, melanogenesis abnormalities, impaired wound healing, and disrupted hair follicle cycling.Clock-regulating pathways—including BMAL1 upregulation, filaggrin/NMF stimulation, RORα/REV-ERBα modulation, and melatonin/antioxidant synchronization—improve collagen synthesis, oxidative stress management, pigment stabilization, and follicle regeneration. Morning application of antioxidants and UV filters enhances photoprotection, while nighttime use of retinoids, ceramide potentiators, melatonin agonists, and DNA repair enzymes aligns with proliferative and lipid synthesis peaks.However, challenges exist: interindividual chronotype variations, limitations of nocturnal rodent models, and lack of biological validation for nighttime applications. Despite these constraints, chrono-cosmetics offer scientifically validated approaches for optimizing dermatological health through temporally aligned therapeutic interventions, representing a paradigm shift in personalized skincare.

Key words : Chronocosmetics, Cutaneous circadian clock, BMAL1–CLOCK signaling, Phase-specific topical therapy, Skin biological rhythms

The skin, being the body's biggest organ, is consistently under external stress such as ultraviolet radiation, environmental pollutants, and chemicals found in beauty products. With the progressing increased lifespan across the globe, the health functionality as well as skin beauty is now given high priority. A significant number of the body's functions that contribute to skin health such as DNA repair, barrier regeneration, and sebum release are regulated by the circadian rhythm.This renders the investigation of skin's biological clock essential for learning when the skin is most susceptible and most responsive to treatment. Consequently, the cosmetic and pharmaceutical industries have directed significant efforts toward helping humans achieve the desirable outcome, like flawless skin. Traditional cosmeceuticals, in general, dealt with the choice of active ingredients. More recent evidence, however, highlights the importance of timing of application as well, since skin penetration and function change rhythmically over the course of the day. This finding has made possible chronocosmetics.

Circadian rhythm is the body's internal phenomenon, regulating the sleep-wake cycle and other behavior patterns of living beings, influenced by external factors such as light and temperature, on a 24-hour cycle. The circadian rhythms have been said to regulate the synchronization of physiologic functions, including the secretion of hormones and metabolism. The circadian rhythms have also been portrayed as changes in the physical, and emotional condition, based on the time.

Other cycles that affect the human organism include ultradian cycles, which occur at a faster pace than circadian cycles and include the 90-minute sleep cycle and hunger cycle. Infradian cycles occur at an extended interval and include the female menstruation cycle, which occurs on an average scale of 28-32 days.

Cosmeceuticals are products coined to mean more than just cosmetics, as they possess therapeutic properties; this term has been in use since the 1980s. Cosmeceuticals form a relatively new field of study that lays the foundation for chronocosmetics, whose application depends on the rhythms of the skin.

Chronocosmetics represent an extension of the cosmeceuticals idea that not only takes into consideration the best time for application but also involves the use of active compounds that work together with the inherent circadian rhythms of the skin in order to enhance the repair and protective functions. The chrono-cosmetics idea represents one of the latest advances in the cosmeceuticals area that combines science and technology with dermatological applications in a manner that combines time sciences with dermatological applications. The high-end strategy employed in chronocosmetics involves consideration and attention to the time of application that is in accordance with the inherent biological time rhythms of the skin. The products employed specialized compounds that were rigorously developed and designed for the purpose of accentuating and harmonizing the inherent circadian rhythms of the skin with the end result being the maximization of repair functions during the night regeneration cycles and during exposure during the day.

"*Zeitgebers*" means "Time Givers,"

which are external environment-related stimuli that drive the body's internal clock cycle. In the emerging new area called Chronocosmetics, these can now be properly categorized under the external *Zeitgebers* umbrella, such as natural regulatory agents like melatonin. The "Dermatological *Zeitgebers*" are a completely novel modality for treatment methods that will have active topically applied molecules acting as a triggering cue for the skin's bodily functions. "Morning *Zeitgebers*" would contain highly potent antioxidant agents like resveratrol, vitamin C, ferulic acid, to name a few, to counter oxidative damage from daylight exposure, thus accentuating the protective mechanism afforded by the skin upon maximum UV exposure during daylight hours at its peak. "Evening/night *Zeitgebers*" would comprise night cream products that contain melatonin,[52] Filaggrin inducers, ceramide boosters, and retinol and retinol-like compounds,[13] which are applied during the night for coordination with the natural repair and regeneration mechanism of the skin, work as night protective zeitgebers and synchronize the night defensive response mechanism. UV protectors and broad-spectrum sunscreens, which are applied during the morning, act as morning protective *zeitgebers* and induce a defensive response during the daytime. Although these cosmaceuticals are not considered traditional zeitgebers, which include environmental cycles of light and darkness, temperature, and eating habits, within the chronocosmetic approach, they are artificial time signals which enhance, repair, and boost the natural biological rhythms of the skin, leading to better dermatological health and resilience. Chronocosmetics and zeitgebers are increasingly being explored for their potential to counteract skin aging, enhance wound healing, and modulate cutaneous inflammation, depigmentation.

Molecular Mechanisms of Circadian Control in Skin :

Circadian rhythms are endogenous biological oscillations with approximately 24-hour periodicity that regulate numerous physiological processes in mammals. These rhythms are synchronized by both photic and non-photic zeitgebers, which serve as environmental time cues to entrain central and peripheral circadian clocks throughout the body.[46] The central pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, receives light information directly from the retina and acts as the master regulator that orchestrates peripheral clocks in virtually all tissues, including the skin.[6] At the molecular level, circadian rhythms are driven by cell-autonomous transcriptional-translational feedback loops (TTFLs) composed of interconnected positive and negative regulatory elements. In the primary feedback loop, the transcriptional activators BMAL1 (Brain and Muscle ARNT-Like 1) and CLOCK (Circadian Locomotor Output Cycles Kaput) form heterodimers that bind to E-box enhancer sequences in the promoter regions of clock-controlled genes.[37] This heterodimerization activates the transcription of Period genes (PER1, PER2, PER3) and Cryptochrome genes (CRY1, CRY2), which encode the core repressor proteins of the circadian machinery. Following transcription and translation, PER and CRY proteins accumulate in the cytoplasm where they undergo post-translational modifications including phosphorylation by casein kinases that

regulate their stability and nuclear entry. These proteins then undergo heterodimerization and translocate into the nucleus, where they inhibit their own transcription by interacting with the BMAL1-CLOCK complex, creating negative feedback. This central oscillating cycle takes roughly 24 h to complete one cycle, hence setting the circadian period. A secondary regulatory circuit provides further regulation through BMAL1-CLOCK-dependent activation of nuclear receptors REV-ERBα/β (Reverse ERB) and RORα/γ (Retinoic acid-related orphan receptor). REV-ERBα/β acts as a transcriptional repressor of BMAL1, while RORα/γ acts as an activator, hence further regulating circadian oscillations by amplitude and period. In human skin, this biological clock regulates various functions such as cell proliferation, differentiation, barrier, DNA repair, and immunity. The skin also has peripheral circadian clocks, which respond to systemic rhythms carried by the signals from the central circadian biological clock of the SCN and also to the ambient stimuli such as fluctuation in temperature and meal times. The genetic Clock mutation, work hours, and even jet lag have been linked to several skin diseases, including dysfunctional skin barrier integrity. Thus, these molecular processes may provide important information regarding chronotherapy, implying the regulation of an optimal time schedule for better skin disorder treatment.

Table-1. Day–Night Skin Biological Rhythm and Targeted Formulation Strategy

Sr. No.	Phase	Clock Biology	Dominant Skin Process	Formulation Priority
1.	Day	PER↑ CRY↑	Oxidative stress defense	Antioxidants, UV filters
2.	Night	BMAL1↑ DNA repair↑	Regeneration, lipid synthesis	Retinoids, peptides, melatonin

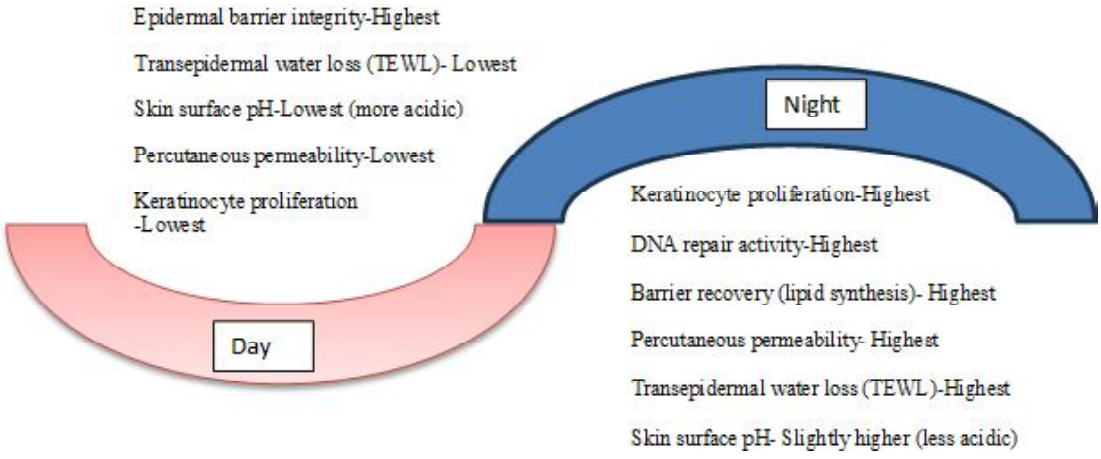

Fig. 1. Day–Night Skin Biological Rhythm

Translational Pipeline for Chronocosmetic Development- The traditional cosmeceuticals have always been based upon a process of development, which can only be put into words with a time-related "one-size-fits-all" formula. As far as the new area of Chronocosmetics is concerned, it is assumed to mean something like this: Our problem is obviously not only with what you put on your face, but with when you put it there, and how this is to be made so that it happens with maximum efficiency right on time according to the clock.

Translation of these clock-aware products is effected in an organized translational process that clearly begins with the molecular level and ends with the personalized therapy process. This is organized and begins with the organized clock gene map wherein the researchers usually identify the cyclic expression characteristics of specific clock-regulating genes specific to each skin cell type. There are different skin cell types in human skin, including keratinocytes, fibroblasts, melanocytes, sebocytes, and those found in the hair follicles referred to as stem cells, which all have distinct cyclical expression characteristics unique to clock genes such as BMAL1, PERIOD, CRYPTOCHROME, REV-ERBα, and RORα. Clock awareness in these fields is essentially the beginning of the road map that leads to therapy.

On this molecular basis, the next step is the identification of therapeutic targets that are specific to the phases. The skin shows an extraordinary circadian rhythm, where the night is characterized by the major focus being on repair, such as the peak of DNA repair, lipid synthesis, or the filaggrin/natural moisturizing factor pathway. At the same time, the day enables the skin to execute defense-related reactions, where the peak of antioxidant enzymes overshadows the diurnal rhythms. The stage of designing represents the interface between biology and the formulation sciences. Instead of designing generic products, the development of chronocosmetics branches off their formulations into morning defensive and nighttime regenerative systems. By doing so, there is no biological phase conflict, wherein substances designed for the nighttime phase could counteract the daytime defense mechanisms, and vice versa. The morning formulations would focus on photoprotective agents and oxidation defense systems, whereas the nighttime formulations focus on renewal substances to facilitate the skin's natural process.

Probably the most innovative areas in chronocosmetic development involve timed-release carrier engineering. Indeed, various sophisticated delivery systems have been developed that respond to circadian cues, such as enzyme-triggered liposomes, pH-responsive microcapsules, and melatonin-synchronised release matrices. These smart carriers are designed to release their active ingredients right at the moment when skin receptivity and repair mechanisms peak to optimize therapeutic efficacy and reduce waste.

The moment of validation brings the temporal considerations right into the clinical trial design of the product. Application timing is rarely considered in traditional dermatological studies, whereas chronocosmetic products need to be validated according to very strict, time-locked protocols. Participants apply products at specific circadian phases, and

outcomes tracked by researchers include not only visible ones but also biomarkers related to circadian rhythms, such as melatonin phase shifts, cortisol rhythm patterns, and oscillations in hair follicle transcript expression. It is this stringent approach that assures the real-world circadian benefits of a product, rather than just those under arbitrary conditions within a laboratory setting.

The last phase accepts the fact that circadian rhythms also differ considerably from one population to another. The issue of chronotypes, morning types, and night owls, for example, may affect the best times to apply the treatments. Apart from that, the effect of age on circadian amplitude and differences in skin patterns due to phototypes would all impact the individual differences with regard to the effectiveness of chronocosmetics. Individualized stratified regimens would be the end result of this chain, with the end products formulated according to these individual circadian differences.

Disease-Specific Chronocosmetic Applications:

1. Skin aging is marked by epidermal thinning, progressive degradation of structural proteins such as collagen and elastin, reduction in melanocyte density, and disruption of epidermal barrier homeostasis. Studies demonstrate that systemic aging is closely associated with circadian rhythm disruption, and similar alterations are observed in the process of skin aging.[15] A healthy circadian rhythm helps the skin repair itself, for example by releasing repair signals that fix DNA damage and protect against UV-related aging.[15] Circadian rhythm-related genes play a major role in regulating pathological processes of skin aging, including oxidative stress, inflammation, and DNA damage.[18,34].

BMAL1 (Basic helix-loop-helix ARNT-like protein 1) and CLOCK (Circadian locomoter output cycles protein kaput) are two major genes involved in circadian rhythm regulation, whose proteins combine to bind a transcription activation complex that results in initiating gene transcription in circadian rhythm.UVB-induced DNA damage in keratinocytes can be repaired more effectively when circadian regulators are modulated, as shown by enhanced BMAL1 activity and suppression of miR-142-3p. (a specific microRNA (miRNA) molecule).This highlights the potential of targeting circadian pathways in chronocosmetic strategies for skin protection and repair[24]

Scutellaria baicalensis extract demonstrates chronocosmetic potential by modulating circadian clock proteins REV-ERBα and BMAL1 to protect against photoaging, suggesting that circadian rhythm regulation could be a novel approach in anti-aging skincare formulations targeting time-dependent skin repair mechanisms.[44] BMAL1 and CLOCK proteins plays important role in regulating UVB-induced apoptosis and DNA damage responses in human keratinocytes.[45]

The PER gene inhibit the expression of BMAL1 and CLOCK with CRY, helping in maintaining the circadian rhythm of skin. Research by Yeom et al. revealed that when PER gene expression decreases, it leads to enhanced skin aging via elevated levels of MMP-1, which breaks down collagen proteins.[12]

MMP1 degrades collagen. There are many studies supporting suppression of MMP1 as a validated antiaging pathway, Topical agents such as peptide nucleic acids and certain probiotic lysates (notably Lactobacillus iners strain KOLBM20) significantly reduce MMP1 expression, increase collagen production, and improve skin parameters in both cellular and clinical studies.[29,30] Downregulation of MMP1 expression mediates the anti-aging activity of Citrus sinensis peel extract nanoformulation in UV-induced photoaging in mice.[7] Collagen homeostasis disturbed is also among the leading causes of skin aging; Ginsenosides enhanced clock gene expression by activating the cAMP/PKA/CREB pathway and preserving collagen homeostasis, hence may act as a potential therapy against skin aging.It is related to the circadian rhythm.[19]

Cutaneous aging is the process of structural and functional changes that clinically translate into visible facial changes. It is also associated with the increased generation of ROS.[1] This results in fine lines, wrinkles, loss of elasticity and volume, rough texture, and uneven pigmentation. Including endogenous tripeptide antioxidant like glutathione which is essential to cellular defense against oxidative stress, and it also acts as a modulator of melanogenesis.[42] Recent reports have pointed out that oral administration of glutathione at a dosage of 250–500 mg/day can lighten the skin and improve parameters such as wrinkles and elasticity.[49]

It was demonstrated that Nobiletin can be used for the potentiation of the defensive systems of the aged epidermis with the use of circadian therapies. It was reported that unbalanced expression of antiviral proteins, combined with distorted BMAL1 and CLOCK clock genes, make the epidermis highly susceptible to viruses.[28] More specifically, among the most significant Candidate Molecules, that are also of great concern in the context of the prevention of viral diseases, is the Nobiletin, which, having the constitutive function of a PMF, targets the circadian functions. The fact that it combines two significant therapeutic functions, the potentiation of the rhythmic immunity of the aged epdermis, the diminution of the viral susceptibility, combined with the suppression of the expression of MMP-9 via the inhibition of p38MAPK signaling, without destroying the collagen, which remains unbroken without impairing the cells, suggests a therapeutic function in combination with its use in the evening to counterbalance the unbalanced expression of MMP in the daytime, in harmony with the nighttime repairs of the epidermis.[26,28]

Temporal Optimization of Anti-Aging Actives-The circadian rhythm in skin physiology is reflected in the temporal efficacy of various anti-aging actives. The gold-standard anti-aging active, retinoids must be used in evening formulations for maximum utilisation of the peak repair window when cellular proliferation is at its peak and the risk of photo degradation is nil. Vitamin C or L-ascorbic acid and vitamin E or α-tocopherol show synergistic photo protection when combined in morning formulations, thus coinciding with peak oxidative stress resulting due to UV and pollution. This time-dependent approach not only leads to maximum therapeutic benefit but also minimum adverse effects, thus clearly showing the practical advantage of chronobiologically informed regimens in skincare.

2. Skin barrier integrity - Balance between repression and gene expression is central to sustaining tissue homeostasis that is lost in the case of injury. To regain the balance we can use biomimetic chronocosmetics that enhances the skin lipid barrier recovery, Lipid lamellae in the stratum corneum are central to skin barrier integrity. Endocannabinoid mediators, notably palmitoylethanolamide (PEA), modulate barrier homeostasis. Moisturizers employing biomimetic technology with physiological lipids and endocannabinoids enhance barrier repair and are effective in managing barrier-disrupted dermatological conditions.[38]

Filaggrin, a key structural protein compacts keratin fibers, flattens corneocytes, and upon degradation generates natural moisturizing factor (NMF). NMF, a hygroscopic mixture of amino acids, urocanic acid, pyrrolidone carboxylic acid, sugars, and electrolytes, sustains skin hydration. Filaggrin deficiency reduces NMF, impairs barrier integrity, increases TEWL, and predisposes to infection, allergen entry, and inflammation.[47] *Cocos nucifera* lipids and glycerine act as biomimetic moisturizers, replenishing physiological lipids and humectants to restore barrier function, by supporting filaggrin-NMF pathways and aligning with circadian barrier repair, they reduce TEWL and inflammation, making them effective chronocosmetic.[3]

A lipid transporter protein primarily found in keratinocytes, ABCA12, make up the epidermis. It is responsible for transporting lipids, such as ceramide, from lamellar granules to the surface of the skin. These lipids are critical for the proper formation of the skin's lipid barrier. The proper transport of lipids by ABCA12 maintains the integrity of the skin barrier, preventing excessive water loss and protecting against dehydration.[27] Chronocosmetic such as Chardonnay grapes extract that support lipid transport is being used in barrier repair of skin.

Compounds such as Epicatechin and Linalool showed strong binding affinity for RORA, which is an important nuclear receptor which is involved in skins circadian regulation, in a study it was found that the activity of BMAL1 was upregulated when cells were treated with Epicatechin and Linalool. Epicatechin and Linalool upregulated skin barrier related and ceramide synthesis genes.[27]

BMAL1 modulates epidermal healing in a process involving the antioxidative defence mechanism, Depletion of BMAL1 delays epidermal healing. BMAL1 expression is circadian, with peak levels during the night-time when epidermal proliferation, DNA repair, and lipid synthesis are maximal; this synchrony is responsible for improved recovery of the skin barrier at night and is the scientific basis for creating night-time directed chronocosmetic products.

3. Acne and inflammation - In a mouse model where skin was treated with Propionibacterium acnes, the clock gene Bmal1, along with its downstream targets Rev-erba, Dbp, Per1, and Cry2, showed reduced expression in skin tissue. This suggests that impairment of Bmal1 signalling contributes to acne-related inflammation.[26]

So, acne is not only a disorder of microbial colonization, overproduction of sebum, or abnormal keratinization but also a

dysregulation involving clock genes. Disruption of circadian rhythm (*e.g.*, jet lag, abnormal sleep) has been shown to enhance acne inflammation through down-regulation of Bmal1.So, in chronocosmetic planning; delivery time and formulation of actives that can reverse or maintain Bmal1/Rev-erba/Per1/ Cry2 expression (or block their suppression) could be a new approach. The complementarity between circadian rhythm and cutaneous inflammation highlights the hopes that can be offered by chronocosmetics. Cosmetics intended to promote the restoration or modulation of Bmal1, Rev-erbα, Per1, and Cry2 gene expression by active ingredients such as melatonin and resveratrol could have anti-inflammatory properties against acne. In addition, the best moment to apply active ingredients relative to the circadian rhythm of the skin, for instance at night when Bmal1 levels are at their maximum intensity, might further improve their efficacy. These findings open a new horizon for the treatment of acne by modulating clock genes that would benefit from further research on the efficacy of chronocosmetics.

4. The production of skin pigmentation is regulated by the usual process that produces the melanin pigment, as well as the body's internal biological clock. The body's 24-hour clock regulates the rhythm at which the pigment cells, also known as melanocytes, work. The BMAL1 clock protein is one of the key regulators that switch ON the genes that code for MITF to produce melanin.When the function of BMAL1 is reduced or compromised, there might be an abnormal increase or reduction in melanin production, giving rise to mottled pigmentation or dark spots.[39]

Chronocosmetic strategy: Using skincare products that take into account the clock of the skin can be quite helpful. For example: Nighttime products using ingredients that stimulate BMAL1 or antioxidation protection can help to modulate melanin production. Day care products using ingredients to protect against the UV and despair DNA can prevent pigmentation damage. Time-release products can release their active ingredients when the skin is best placed to heal itself, adding to their effectiveness, according to their product action synchronizing with the best action of the skin. Chronocosmetics can prevent as well as correct dark spots and uneven skin color.

Glutathione, a powerful antioxidant, inhibits tyrosinase activity and promotes lower melanin production, as it increases the amount of pheomelanin by reducing oxidative stress, which affects melanin production The complementarity between this treatment criterion and the chronocosmetic component certainly increases the effect of the process of depigmentation, because the release of melanin also presents a circadian nature, which naturally decreases throughout the night after the repair of the skin. The application of glutathione cosmaceuticals at night represents the regeneration of the skin that happens at night, coordinating the mechanism of the antioxidant system with the pigmentation process, which is governed by MITF, tyrosinase, TRP-1, and TRP-2.[4]

5. Hair and Scalp Health- Topical melatonin is a pragmatic chronocosmetic candidate to improve hair health and pigmentation by merging follicular clock biology with antioxidant and receptor-mediated actions. Hair follicles express core clock genes (CLOCK, BMAL1, and PER1) that gate melanocyte

activity and hair-cycle transitions; the disruption of the latter increases tyrosinase/TRP expression and follicular melanin synthesis, establishing a mechanistic link between circadian timing and pigmentation.[11] By aligning topically administered melatonin to its endogenous nocturnal peak, night-aligned melatonin leverages endogenous nocturnal peaks by engaging MT1/MT2 receptors to promote anagen duration, reduce oxidative damage to melanocyte stem cells, and modulate various signalling pathways (AKT/β-catenin and Nrf2) important for preserving the integrity of the pigmentary units.[16] Clinical pilot trials describe increased anagen hair rate and improved hair density with once-daily topical melatonin (0.1% solution) and favourable tolerability, supporting the translational potential of this approach.[41] However, chronocosmetic formulation strategies may further maximize follicular receptor engagement during repair phases. Nocturnal application, controlled-release systems, or receptor-targeted prodrugs may minimize daytime photo degradation and synergize with systemic circadian cues to protect follicular melanocytes. In other words, melatonin represents a mechanistically grounded, clinically supported chronocosmetic strategy for improving hair growth and stabilizing pigmentation when timed to the follicle's circadian biology.

Hair Growth – Cycling of hair follicles is also strictly controlled by circadian rhythms, in which the combined effect of the BMAL1, CLOCK, and PER1 clock genes controls the regulation of anagen, catagen, and telogen phases of hair follicles[33,48]. Disregulation of these molecular clocks leads to an absence of normal cycle patterns of hair follicles and consequently leads to early hair loss. In ex vivo studies, BMAL1 and PER1 repression was found to extend the anagen phase, meaning the regeneration capacity of the hair follicle is already preset by the circadian system itself[5]. Moreover, the circadian clock also controls the processing of anagen because the secretion of melanin in melanocytes of hair follicles is dictated by the BMAL1 and PER1 signals [32].Recent studies also bring into prominence the role of melatonin in controlling the hair cycle because of its twin role in regulating the molecular clock and stimulating the regeneration of hair follicles.Melatonin acts on dermal papilla cells via the Wnt/β-catenin pathway to increase the secretion of Wnt ligands and result in the induction of anagen hair growth[20]. This points to the use of melatonin as a potential chronocosmetics molecule through the convergence of the circadian gene/ CANONICAL Wnt pathway.Melatonin's action on CLOCK-BMAL1 transcriptional activity synchronizes local follicular oscillators to systemic circadian cues, re-establishing temporal homeostasis compromised by stress, light exposure, or aging. There exists an accumulative body of evidence that gives a positive indication of using chronobiologically active agents like melatonin, ginsenosides, and/ or resveratrol in the context of chronotherapeutic scalp cosmetic treatments. The imposition of these APIs on "dermatological zeitgebers" could be a paradigm shift in the formulation of "trichoccosmetics"—a blend of timing, molecular biology, and formulation sciences that could unlock the best follicular response through circadian entrainment.

6. Wound Healing and Tissue Regeneration-There are some documented examples of how the abnormality of the circadian rhythm

can be a contributory factor in the healing of the wound. Abnormal circadian rhythm results in an abnormal healing process. It is the process that expresses and represses genes to ensure the attainment of tissue homeostasis, but in the process, there is an abnormality due to the presence of a wound. BMAL 1 is involved in epidermal healing process[35] Depletion of BMAL1 delays epidermal healing. Other genes like PER, CRY, REV-ERBα are also involved in this process, scientists used synthetic molecules to manipulate these clock genes and improve healing outcomes; Xue *et al*.[40] probed the potential of two synthetic circadian modulators in corneal wound repair: KL001, a Cryptochrome that lengthens circadian periodicity, and SR8278, a REV-ERBα antagonist that de-represses clock-controlled genes. These molecules showed that timing modulation of circadian machinery—either by lengthening regenerative phases (KL001) or reversing inhibitory signals (SR8278)—can improve healing outcomes at certain zeitgebers times.

Future Directions :

The next wave of chronocosmetics has to move from proof-of-concept entrainment to mechanism-informed, time-resolved interventions targeting selectively the molecular clock nodes in the skin compartments. Key research activities include the development and topical optimization of selective clock-modulators-REV-ERB/ROR modulators, melatonin analogs, SIRT1/NADz modulators, and RNA-based regulators-engineered for epidermal penetration and phase-specific activity-combined with controlled-release platforms (light-, pH- or enzyme-triggered carriers and timed nanoparticles) that temporally match payload delivery with endogenous repair peaks[50,12]. Empirical programs demonstrating translational value will need to link robust molecular endpoints-Per/Cry/Bmal1 oscillations, NADz /SIRT1 dynamics, and DNA-repair signatures-with clinically relevant outcomes such as barrier recovery kinetics, UV-damage clearance, timing of pigmentation, and (stem-cell-mediated) regeneration, leveraging evidence that epidermal clocks drive diel repair and regeneration programs[12].

Standardization now needs to be ensured on the following lines: validated human chronobiomarkers, harmonized *in vivo* circadian end-points, and randomized chrono-clinical trials which control for chronotype, environmental zeitgebers and cosmetic matrix effects are necessary[12,17].

Chronotherapeutic approaches should be explicitly tested as combination regimens including chrono-timed antioxidants, DNA-repair enhancers, and anti-inflammatories, co-administered with lifestyle entrainment measures such as sleep hygiene, timed light exposure, and meal scheduling to amplify local circadian synchronization and sustain clinical efficacy.

Finally, it must be concluded that this area must also focus on many issues that still need to be open researched: What nodes of the clock of the skin can be intervened on in a way that avoids chronodisruption? What time of exposure can be balanced in order to favor repair time and oncogenes risk? How to stratify the patients for chronotype, age, and phototype to adjust to personal chronoregimes? The resolution of this set of issues will launch the chronocosmetic field to the science of reality,

leaving behind the commercial story[22,43].

Challenges in Chronocosmetics Development and Application :

Chronocosmetics face a series of challenges, both from a scientific point of view and a practical one. The easy application of scientific knowledge to their use by consumers is barred on all sides. This would be true in the preclinical models and consumer behaviour.

1. Translational and Preclinical Challenges-The circadian literature is dominated by work performed in nocturnal rodents that have activity and rest cycles that are reversed relative to humans. This has led to a reciprocal difference in peak expression times for core clock genes such as BMAL1 and CLOCK to be at different times in rodents than in humans, thus making it very difficult to extrapolate timing for optimal intervention times[9]. The reversal achieved through light and dark housing systems is prone to certain logistical and economic challenges despite all that is aimed at fully approximating human diurnal photoperiod entrainment. The skin circadian system is heterogeneous. Each type of cell has a specific pattern of circadian gene expression, and this suggests that there is a specific moment for each skin layer to be repaired, proliferated, and modulated to reduce inflammation. This heterogeneity in circadian rhythm affects the possible feasibility of single-phase chronocosmetics that treat skin and underlying tissues in harmony. It is even further affected by basic cycles such as the cycle of the follicle and amplitude reductions in basic clock genes that undermine a priori timing information for active ingredient response in skin affected by weakened circadian rhythms associated with increasing age[25].

2. *Challenges in Formulation and Delivery Systems:* Chronocosmetics need the precise timing of ingredient availability. "Day-phase" ingredients like UV filter substances and "antioxidant stabilizer" ingredients help protect the skin from the sun's exposure, while "night phase" ingredients such as "retinoids" or "epidermal growth peptides" along with "DNA repair enzymes" target the period of highest mitoses. It does not make biological sense to mix these kinds of ingredients in a single product with a 24 hour cycle[36]. Intelligent delivery systems such as liposomes, polymeric microcapsules, or enzyme-triggered carriers are needed for timed release, actuated by diurnal biochemical cues[21].

3. Clinical and Consumer Implementation Barriers - Chronotherapy success depends upon an individual's biological circadian phase, which naturally varies because of sleep schedule, age, shift-work exposure, and chronotype. The gold-standard measure, dim-light melatonin onset, requires controlled light conditions and multiple timed saliva collections and hence is impractical to use for cosmetic personalization. Efforts to develop accessible biomarkers include cortisol in sweat, core body temperature rhythms, and hair follicle transcript profiling, but these are not yet validated for home-use kits[21,23]. Without simple phase-tracking, precision-timed application remains theoretical. In addition, consumer compliance is optimized for routine-based usage (*e.g.*, "morning" and "night"). Requiring precise application timing-including "within 90 minutes of habitual sleep onset"-introduces behavioural friction that constitutes a major commercialization barrier.

4. Regulatory and Economic Barriers- Chronocosmetics represent a regulatory grey area between cosmetics, which require only limited safety data, and drugs, which must demonstrate efficacy. Products making claims for "clock gene expression modulation" or "DNA repair timing enhancement" may be considered drugs in some jurisdictions, such as the FDA or EMA, necessitating expensive preclinical toxicology and Phase I-III trials. The lack of clarity in the rules governing chronocosmetics contributes to a negative effect on the investment of the R&D of chronocosmetics. Secondly, two-phase formulations of AM/PM cosmeceutics result in higher costs of production by two times as compared to single-product lines.

Chronocosmetic applications offer a direct utilization of circadian science principles to dermatological treatments and prove the relevance of the timing of product use equally to the composition itself. All of the above biological events of DNA repair, lipid synthesis, barrier repair, melanin synthesis, inflammation response, and follicular cycling follow a predictable cyclic rhythm in the body. The strategic utilization of these opportunities has shown beneficial effects of antioxidants and photoprotectants corresponding to day-time protection phases and simultaneous use of retinoids, ceramide potentiators, melatonin agonists, and DNA repair agents corresponding to night-time repair phases of the skin.

However, its translation into standardized practice is currently still in its infancy. Variability of chronotype, as well as the lack of suitable human chronobiomarkers and appropriate time-resolved clinical trials, prevents a high degree of personalization. Future advancements will be necessary within phase-specific delivery systems, clock-targeted actives, and within the development of diagnostic tools that support a precise determination of one's personal circadian phase. Chronocosmetics is definitely not just a fashion phenomenon, as it is a science-driven approach that has high potentials when merged with powerful formulation and personal timing.

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