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Highlights

Rhythms under tension: Circadian clocks in an Unsynced Society

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ABSTRACT

This special issue of the *Biomedical Journal* centers on circadian rhythms, examining the molecular mechanisms of the circadian clock, the consequences of circadian disruption, and their implications for health and disease. Featured topics include blue light therapy for sleep disorders in myocardial infarction patients; sex-specific links between clock genes and colorectal cancer; the impact of social jetlag on blood pressure; and how irregular light-dark cycles and misaligned eating patterns affect circadian stability. A study on Stenabolic (SR9009) in mice investigates its potential to mitigate weight gain, insulin resistance, and white fat accumulation under constant light exposure. Additional reviews address the role of purinoreceptors in extracellular vesicle-mediated communication, the evolving understanding of pseudogenes and their functional derivatives, and future prospects for hyperpolarized magnetic resonance imaging. Original research highlights the influence of corticosterone on white adipose tissue expansion in mice and challenges the assumed protective role of pentoxifylline against diabetic retinopathy in patients with chronic kidney disease and diabetes. A novel application of peripheral magnetic stimulation as a treatment for overactive bladder is also explored. Two studies on hidradenitis suppurativa are included: one linking the condition to an increased risk of migraine in women, and another examining its association with alopecia areata. The issue concludes with two letters to the editor on the effects of the SARS-CoV-2 spike protein on erythrocyte biology, along with a request for further clarification, which is addressed in detail.

1. Spotlight on reviews

1.1. Swing of time

Under British colonial rule in India, the punkah wallah or punkah puller became a designated occupation. These low-paid, often exploited laborers operated ceiling fans, punkahs, in the grand homes of European masters. Prior to the advent of electric, a manual pulley system was used. Punkah pulling was relegated to the lowest rungs of the service hierarchy, regularly subjecting workers to racial violence. Preferably individuals with visual or hearing impairments were assigned this task to accommodate the rulers' desire to avoid eavesdropping. For added privacy, ropes were threaded through wall holes, enabling the punkah to be manipulated from outside the bedroom.

This role required continuous effort, day and night. Colonial households were troubled by sleep disturbances due to unfamiliar foods, unfamiliar weather, diseases, environmental noise, and insects, depended heavily on punkah pullers for nighttime comfort. Poor sleep among British colonizers was frequently recorded along with the resulting frustration and fatigue, which affected administrative efficiency. When punkah pullers—already exhausted from household chores—fell asleep in the middle of the night and the fan ceased, colonist masters would often respond with violent outbursts, sometimes even causing the worker's death. Myths circulated that some punkah pullers had trained themselves to swing the rope with a specific jerking motion using their big toe while asleep, an ability used to justify continued manual labor by claiming the movement was impossible to be mechanically replicated. This myth, however, was dismissed by engineering authorities [1]. [1] [2] [3]

Punkah pulling shifts at night commonly lasted 8–12 hours but were often executed in addition to other domestic tasks during the day. Inhumane methods were often used to keep workers awake: sugar scattered around the worker to attract ants, or live ducks or geese placed under their arms, with punishment if the animals were released.[4]

1.2. Bound to rhythm: the molecular clock

Today, sleep disruption is widespread and recognized as both a cause and consequence of circadian misalignment. It is driven by long work hours, lifestyle factors, and the pervasive use of artificial light-emitting devices. Although once believed to be reversible, some of these

[1] https://en.rattibha.com/thread/1672466460659298305, last access 05/04/2025.
[2] https://servantspasts.wordpress.com/2020/08/10/the-punkah-and-its-pullers-a-short-history/, last access 05/04/2025.
[3] https://scroll.in/article/1028513/amidst-uk-heatwave-a-reminder-of-how-british-colonials-exploited-punkah-walas-in-indias-summers, last access 05/04/2025.
[4] https://mail.satyaagrah.com/history/britishers/2806-punkah, last access 05/04/2025.

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impairments persist and individuals may underestimate the effects of accumulated sleep loss over time. Sleep loss causes *inter alia* reduced mood, neurobehavioral dysfunction, performance deficits, and neuron loss in areas linked to vigilance and episodic memory. Those changes are now known to be lasting. Sleep deprivation may also contribute to aging and exacerbate neurodegenerative processes [2].

The circadian clock, an internal timekeeping system, offers organisms a fitness advantage by enabling them to anticipate environmental changes particularly to those related to the day-night cycle. Chronobiology encompasses such rhythms across different timescales: high-frequency, e.g. hormone secretion pulses throughout the day; circadian, e.g. activity and rest cycles; and monthly or annual cycles, e.g. reproductive or seasonal cycles [3].

At the molecular level, circadian clocks are cell-autonomous, and circadian rhythms are generated through transcriptional-translational feedback loops (TTFLs). The CLOCK and BMAL1 proteins form a complex that activates the transcription of Period (PER) and Cryptochrome (CRY) genes via E-box elements. PER and CRY proteins eventually inhibit CLOCK/BMAL1, establishing an oscillatory feedback loop. Additional loops involving REV-ERBα/β repressors and RORα/β activators help regulate BMAL1 expression, while *Dbp*, another CLOCK/BMAL1 target, contributes to rhythmic transcription.

Light acts as a primary Zeitgeber (time giver), detected by melanopsin in intrinsically photosensitive retinal ganglion cells (ipRGCs). These cells project to the suprachiasmatic nucleus (SCN), the master circadian clock in the brain. Melanopsin levels rise with light exposure and fall in darkness. Melanopsin also controls other light-responsive biological processes such as melatonin synthesis, glaucoma development, and sleep. The SCN synchronizes peripheral clocks via neural and hormonal signals, though peripheral clocks can also function independently. In the absence of a functioning SCN, peripheral clocks can still entrain, underscoring the SCN's role in maintaining rhythmicity under disrupted or absent Zeitgeber conditions [4–8]. Additional Zeitgebers include the timing and composition of meals. Eating at biologically inappropriate times can misalign internal clocks, contributing to obesity and metabolic dysfunction [9].

1.3. Circadian Drift

Circadian clocks are essential for systemic homeostasis and maintain rhythm under constant conditions. However, without regular entrainment, they lose the ability to accurately predict environmental changes. Chronotypes (individual circadian phases) vary widely due to genetics and environmental factors like seasonal light variation [11].

Disruption of the circadian clock occurs, for instance, in the presence of conflicting cues leading to incompatible processes happening simultaneously. British colonizers in India experienced significant circadian disruption due to geographic relocation, changes in diet, and altered environmental cues. Enslaved or indentured individuals such as the punkah pullers suffered from extreme sleep deprivation, nutritional deficits, and disordered schedules. These conditions severely impaired circadian regulation, likely affecting both physiological resilience and long-term health.

Relatively recent changes to our environments, such as the introduction and increased daily use of artificial lighting, can disorganize the circadian system down to the level of molecular clocks. Artificial light at night (ALAN), while a major technological advance, has not only become a form of environmental pollution, but also a major source of circadian disorganization. ALAN disrupts the circadian regulation of hormones, cell cycles, and metabolism, particularly due to blue light exposure from LEDs and electronic devices, wavelengths, that strongly suppress melatonin production [12–14]. Circadian misalignment also affects bone health, increasing fracture risk in night shift workers, and may cause sustained skeletal effects when it occurs during adolescence [15]. Moreover, it contributes to metabolic dysfunction by disrupting appetite-regulating hormones, energy expenditure, and increasing obesity risk [16].

1.4. Broken rhythms

As illustrated in [Fig. 1], Martel et al. examine the regulation of the human circadian rhythm in this issue of the *Biomedical Journal*. They also provide insights into how factors such as artificial light, nutrition, physical activity, and aging interact with the circadian system to influence health and disease. For instance, red wavelengths do not suppress melatonin production, unlike the blue and white light predominant in LED sources.

Martel and team advocate for accessible interventions to reduce circadian disruption. They highlight the largely neglected influence of electromagnetic fields (EMFs) on circadian rhythms. EMFs can alter the structural order of intracellular water, affecting charge separation and cellular bioelectric properties. Structured water, which is more viscous than bulk water, supports various cellular functions and may be sensitive to EMF exposure [10].

Diminished exposure to red and infrared light from sunlight, combined with constant EMF exposure, may reduce melatonin production and impair mitochondrial efficiency. Red light at 670 nm, also used in light therapy, has been shown to lower mitochondrial viscosity and enhance ATP production by improving ATP synthase motor performance. Disrupted protein hydration and phase separation dynamics, potentially driven by circadian misalignment, have been proposed as key contributors to neurodegenerative diseases such as dementia [17].

Chronomedicine, a growing field, incorporates circadian principles into clinical practice. This includes strategies such as scheduled light exposure, melatonin supplementation, and structured routines based on Zeitgeber. These approaches can improve symptoms and quality of life in individuals with neurodegenerative diseases including Alzheimer's, Huntington's, and Parkinson's [18–21]. Further articles in this virtual special issue about circadian rhythms explore the potential of circadian-based interventions in managing cardiovascular events, metabolic disorders, cancer, and inflammation.

2. Also in this issue

2.1. VSI: circadian rhythms

2.1.1. Living offbeat

In the editorial to this VSI of the *Biomedical Journal*, Martel, Ojcius, and Young highlight the growing dissonance between innate circadian rhythms and a lifestyle increasingly shaped by prolonged exposure to artificial light. Such disruption of biological rhythmicity negatively impacts cardiovascular health and metabolic function. Circadian rhythms, they emphasize, govern far more than the sleep-wake cycle, influencing hormone secretion, metabolism, immune function, energy homeostasis, motor coordination, and tissue repair. Interventions that preserve or restore circadian alignment hold promise in preventing and treating a wide range of conditions. Disruptions, commonly caused by sleep deprivation, night shift work, or frequent time zone changes, can compromise systemic health. Since sunlight acts as the primary synchronizer of circadian timing, regular exposure to natural light, a habit diminished by modern indoor lifestyles, may reduce the incidence of cancer, hypertension, cardiovascular disease, multiple sclerosis, Alzheimer's disease, and myopia [22].

2.1.2. Heart in blue

In a randomized, placebo-controlled study, Chin et al. studied the effects of light therapy on sleep quality and clinical outcomes in patients with myocardial infarction (MI). Compared to healthy controls, MI patients exhibited poorer sleep and significantly lower vitamin D levels [23]. Reduced vitamin D levels may result from inadequate ultraviolet-B (UVB) exposure, which is limited by geographic and seasonal factors. Effective sunlight exposure typically occurs between 10 a.m. and 3 p.m.

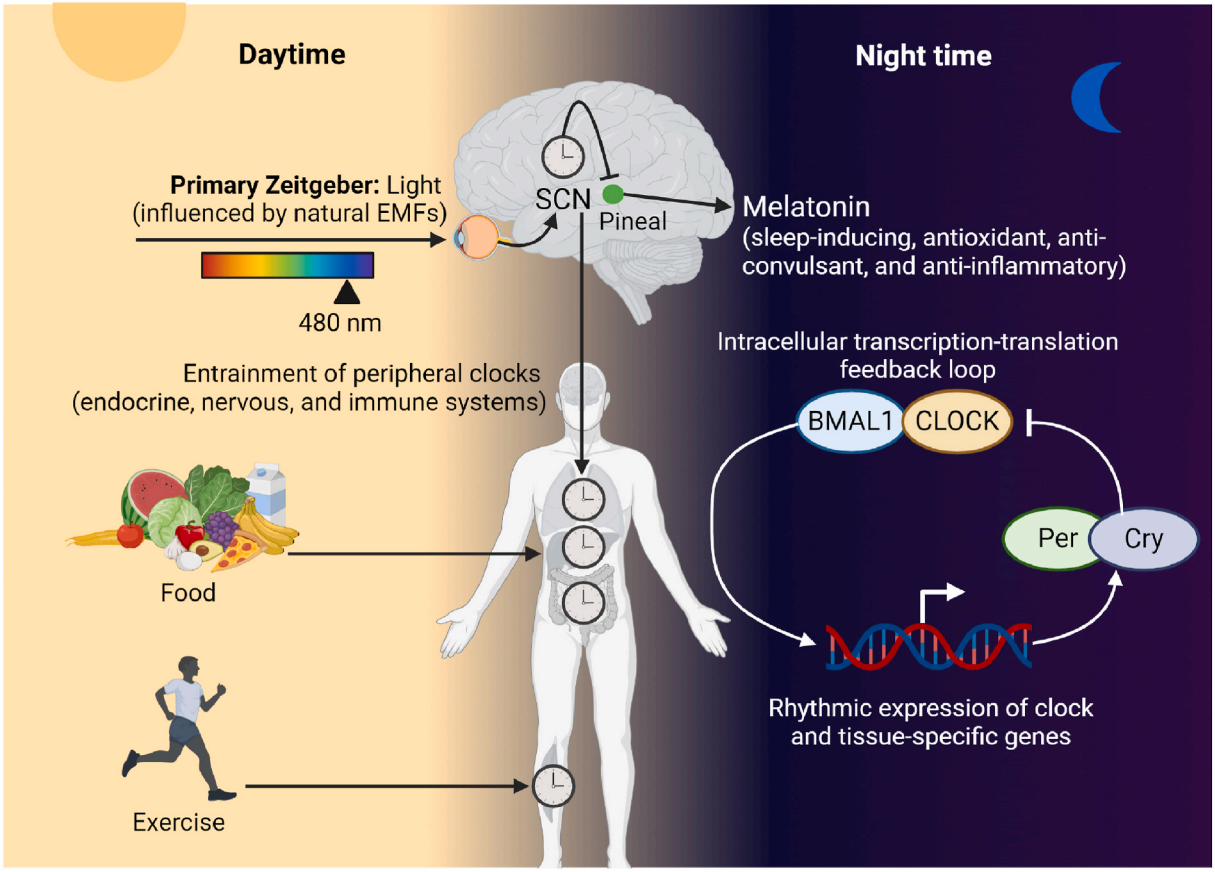

Fig. 1. Multi-factorial entrainment of the circadian system by light, food, exercise, and electromagnetic fields (EMFs). Light entrains the circadian clock in the suprachiasmatic nucleus (SCN), which synchronizes hormone production and peripheral clocks via the autonomic nervous system. Light also inhibits melatonin production by the pineal gland. Food and exercise influence circadian clocks in peripheral tissues. Key clock genes and proteins include CLOCK and BMAL1, which activate transcription of PER (Period) and CRY (Cryptochrome), forming a core feedback loop that generates circadian oscillations(Figure by Martel et al. [10]).

Additionally, conditions such as intestinal malabsorption or hepatic and renal insufficiencies can further impair vitamin D production [24].

While blue light therapy had only a modest impact on sleep quality, it significantly increased vitamin D levels compared to white light. MI patients also presented with higher rates of obesity and comorbidities, including renal and liver disease [23].

2.1.3. Gendered clockwork in cancer

Shift work has been linked to increased cancer incidence, potentially due to melatonin's role as a major scavenger of reactive oxygen species (ROS) [11]. Additionally, PER proteins are implicated in oncogenesis, with single nucleotide polymorphisms (SNPs) in BMAL1 and CLOCK, as well as certain PER/CRY genes, correlating to an elevated cancer risk [25].

Sex differences play a critical role in the development of many cancers, influencing incidence, prognosis, and mortality. Key genes involved include those related to immune function, metabolism, DNA repair, and sex chromosomes [26].

Herichová identified sex-biased, cancer-promoting microRNAs (miRNAs) associated with clock genes per2 and/or cry2 that contribute to the sex-dependent development of colorectal cancer (CRC). In men, up-regulated miRNAs predominantly promote tumors by inhibiting phosphatase and tensin homolog (PTEN)- and p53-mediated regulation of the cell cycle, while also decreasing the expression of the tumor suppressor gene per2 in CRC tissue [27].

2.1.4. Sunglasses at night

Do you think, social jetlag is just a minor inconvenience? Otsuka et al. shed light on the hidden costs of irregular schedules, particularly at night, and their effects on cardiovascular health. In their study of Japanese women, they conducted 24-h blood pressure (BP) monitoring over seven days to examine both internal and external desynchronization caused by social jetlag with a focus on within-day and between-day BP variations. Their findings provide valuable insight into the operation of multiple circadian clock components. The study suggests that even short-term social jetlag is linked to an increased risk of cardiovascular events. Adaptation to a desynchronized state occurs unconsciously, driven by large-scale brain networks. Specific cells in the suprachiasmatic nucleus (SCN) active during the day and night may play a central role in this biological clock-guided integration [28].

2.1.5. Time to eat

Recent research highlights a complex relationship between circadian rhythms and gut microbiota, where disruptions to the body's internal clock can negatively impact microbiota composition and diversity via the gut-brain axis [29]. Seasonal sun exposure has been shown to enrich the skin microbiome [30], which plays a crucial role in immune, endocrine, and nervous system function. Loss of biodiversity or dysbiosis in the skin and gut microbiomes may contribute to the development of chronic diseases. Disruptions of the gut-skin axis are also implicated. These imbalances have been linked not only to skin conditions, but also to diseases not traditionally associated with the skin, such as cardiovascular disease and Parkinson's disease. A modern lifestyle, characterized by stress, poor diet, and limited exposure to natural environments, is believed to exacerbate these imbalances [31].

Tomas et al. review evidence showing that irregular light-dark exposure and misaligned eating patterns cause desynchronization of the suprachiasmatic nucleus (SCN) and peripheral clocks. These

circadian disturbances promote gut microbiome dysbiosis, which in turn contributes to metabolic dysfunction, inflammation, and cancer. The review also explores how circadian interventions like intermittent fasting (IF) may help mitigate risks for diabetes, cardiovascular, immunological, neurodegenerative, and cancer-related diseases [32].

2.1.6. Rhythm of the night

Exposure to continuous light is known to suppress pineal activity and inhibit pineal melatonin production, which normally peaks during the dark phase of the circadian cycle. Plasma melatonin follows a circadian rhythm, with high levels at night and low levels during the day [33].

The synthetic compound Stenabolic (SR9009), a REV-ERBα/β agonist, enhances Rev-erb gene activity and suppresses BMAL1 expression, thereby stabilizing intrinsic circadian rhythms. Yang et al. examined the effects of SR9009 in a model of circadian disruption, simulating conditions experienced by individuals under long-term rotating or night shift work. Mice exposed to constant light exhibited increased body weight, insulin resistance, white fat mass, and altered circadian clock gene expression. Treatment with SR9009 reduced weight gain, insulin resistance, and white fat mass, though it had no effect on overall energy homeostasis. Expression of REV-ERBα/β in white and brown adipose tissue was restored, indicating the potential of SR9009 as a therapeutic strategy for counteracting metabolic effects induced by circadian misalignment [34].

2.2. Review articles

2.2.1. Relay systems of communication

Early forms of long-distance communication presented a real challenge for our ancestors. Sound waves produced by crafted instruments and capable of traveling across great distances offered a natural solution. Among the most widespread instruments were slit drums, independently developed by Indigenous cultures across Africa, Oceania, Central and South America. Slit drums were not only used in spiritual and social gatherings, but also as tools for transmitting messages. Important events including births, deaths, communal meetings, as well as urgent warnings of danger were announced through drummed signals. Mastering such communication required more than musical skill: crafting the drum, striking it in specific ways, choosing the pitch, even the time of day - all could influence transmission. Terrain and weather conditions added further complexity. To extend their reach, drums were often used in relay-like networks, passing messages from one village to the next, thus drastically reducing the time needed for long-distance communication. [5] ,[6],[7]

In a biological counterpart to these ancient networks, extracellular nucleotides, primarily ATP, but also ADP, UTP, UDP, UDP-sugars, adenosine, and adenine, mediate purinergic signaling, a ubiquitous system of cell-to-cell communication [35]. As reviewed by Duret et al., purinoreceptors play a central role in regulating communication via extracellular vesicles and shaping the responses of recipient cells. P2 receptors vary in their selectivity and sensitivity, activating distinct secondary messengers and signaling pathways. Together with ectonucleotidases, these receptors govern key aspects of extracellular vesicle biology, its biogenesis, degradation, and even molecular content, forming a complex, dynamic system for long-distance cellular communication [36].

2.2.2. Buried Riches

Terra Preta, or Amazonian Dark Earth, is a remarkably fertile soil that challenges assumptions about tropical soil infertility. Found in regions typically dominated by heavily weathered, nutrient-poor clay soils, it displays unusually high fertility and elevated pH levels. Archaeological evidence suggests these anthropogenic soils were created over millennia by indigenous populations in the central Amazon. With the arrival of Europeans and the resulting collapse of those societies, the production of Terra Preta ceased, and the sites were gradually overtaken by forest. Uniquely rich in nutrients, Terra Preta is believed to have supported dense populations through intensive agriculture. During early colonial exploration, Spanish Conquistadores dismissed reports of such productivity, claiming Amazonian soils could not sustain large communities. These prevailing beliefs, rooted in a disregard for indigenous agricultural innovation, contributed to the loss of knowledge surrounding Terra Preta's creation. Today, its capacity to support robust plant growth is recognized, and its potential role in carbon sequestration has attracted interest for climate change mitigation. [8], [9],[10]

Similarly, once-dismissed genetic elements have resurfaced in scientific attention. Long labeled "junk DNA," these sequences were believed to serve no functional purpose. This view has shifted with the recognition that many pseudogenes are transcribed into RNA and some may even encode functional peptides or proteins [37]. Lin et al. review the growing evidence suggesting pseudogenes and their derived functional molecules participate in diverse biological processes and may serve as prognostic markers in cancer [38].

2.2.3. Spinning into a New era

Magnetic Resonance Imaging (MRI) is not only a widely used, non-invasive diagnostic tool. It is known for its versatility, though limited by long acquisition times, variable tissue sensitivity, and patient discomfort [39]. Hyperpolarized (HP) MRI enhances nuclear spin polarization, providing a high-contrast alternative to standard proton MRI [40]. This approach enables applications such as real-time enzymatic activity measurement and has been used in studies of neurological disorders [41].

Hsieh et al. discuss recent developments in HP MRI, detailing polarization techniques as well as the modality's expanded diagnostic potential beyond conventional MRI and positron emission tomography (PET). The research team also focuses on current challenges including short imaging windows, complex preparation, and data processing. They point to future directions involving AI integration, protocol standardization, and novel tracer development [42].

2.3. Original articles

2.3.1. Fat, stress, and the silent catalyst

Previously, chronic administration of corticosterone, the principal glucocorticoid mediating stress responses in rodents, was shown to induce obesity, elongation of the small intestine, hepatic steatosis, and elevated serum insulin and leptin levels, implicating glucocorticoids in stress-associated obesity [43].

Tsai et al. had earlier developed a mouse strain with normal baseline corticosterone (CORT) levels that remain unresponsive to high-fat diet (HFD) exposure. In this model, HFD-induced fatty liver was attenuated compared to wild-type mice, and this phenotype was reversible with CORT supplementation [44].

In their current study, Tsai and colleagues used the same mouse

[5] https://organology.net/instrument/slit-drum/, last access 05/10/2025.

[6] http://www.philtulga.com/Talking%20with%20Drums.html, last access 05/10/2025.

[7] https://www.academia.edu/34516522/African_Drum_Telegraphy_and_Indigenous_Innovation_African_Contribution_To_Communication_Science, last access 05/10/2025.

[8] https://www.intechopen.com/chapters/73242, last access 05/10/2025.

[9] https://www.bbc.co.uk/science/horizon/2002/eldorado.shtml, last access 05/10/2025.

[10] https://www.science.org/content/article/ancient-amazonians-created-mysterious-dark-earth-purpose, last access 05/10/2025.

model to investigate whether diet-induced CORT influences white adipose tissue (WAT) expansion. Building on prior evidence suggesting that HFD-induced corticosterone promotes lipid uptake into storage organs, they now show that this effect may be mediated through enhanced adipogenesis. Specifically, they observed CORT-dependent down-regulation of Pref-1 [45], a key inhibitory factor in the differentiation of preadipocytes into mature adipocytes [46].

2.3.2. *Extraterrestrial origins and earthly side effects*

All terrestrial life relies on nucleic acids, which store genetic information through pyrimidine and purine nucleobases. The origin of these nucleobases remains under debate, though carbon-rich meteorites are considered potential sources of essential organic compounds for early Earth. It is hypothesized that nucleobases may have arrived via extraterrestrial material, including comets, asteroids, their fragments, and interplanetary dust. Purines such as hypoxanthine and xanthine, though absent from DNA and RNA, serve as key intermediates in purine nucleotide metabolism [47,48].

Stimulants derived from Xanthine include caffeine, theobromine, and theophylline.[11] Pentoxifylline, another xanthine derivative, is used to treat peripheral vascular disease. As a phosphodiesterase inhibitor, it enhances blood flow by decreasing viscosity and increasing red blood cell flexibility.[12]

In a multi-institutional cohort study, Lin et al. evaluated the association between pentoxifylline use and diabetic retinopathy (DR) in patients with chronic kidney disease (CKD) and diabetes mellitus (DM). Although pentoxifylline was assumed to prevent diabetic retinopathy (DR) by improving capillary perfusion, the study found otherwise. Regardless of whether patients already had DR, its use was associated with an increased risk of the condition in individuals with chronic kidney disease (CKD) and diabetes mellitus (DM), highlighting the need for cautious therapeutic use in this group [49].

2.3.3. *Magnetic precision in peripheral neuromodulation*

Electromagnetic stimulation offers a non-invasive therapeutic avenue across various physiological systems. Magnetic stimulation is well established in neuromodulation, especially in the brain. Protocols like intermittent theta burst stimulation (iTBS), a patterned form of repetitive transcranial magnetic stimulation (rTMS), show promise in conditions such as autism spectrum disorder due to their brief duration and lower intensity [50]. Low-energy shock wave (LESW) therapy has demonstrated the ability to suppress bladder overactivity in a rat model of chemically induced cystitis, with observed reductions in inflammatory markers [51].

In a novel application, Khasanah and colleagues investigated repetitive peripheral magnetic stimulation (rPMS) combined with iTBS on the sacral roots, identifying stimulation parameters with potential therapeutic effects for overactive bladder (OAB). Using a defined rPMS protocol, the team demonstrated suppression of acetic acid-induced bladder overactivity in rats, achieving significant improvements through precisely timed stimulation pulses. Khasanah et al.'s work represents the first *in vivo* demonstration of sacral rPMS-iTBS effectively suppressing bladder overactivity through peripheral neuromodulation, suggesting a potentially viable non-invasive modality for OAB management [52].

2.3.4. *From skin …*

Since antiquity, traditional medical systems such as Ayurveda, Chinese Medicine, and Unani (Greco-Arabic or Islamic) medicine have employed a wide array of herbs and plants to maintain the cleanliness and health of skin, hair, and teeth. These were administered as decoctions, juices, and pastes, often using natural surfactants [53].

In Sri Lanka, 133 plant species from 64 families have been documented in Ayurvedic cosmetic applications [54]. Today, researchers are revisiting specialized botanical formulations to address challenges like hair loss arising from stress, illness, genetic predisposition, and other causes [55].

Ayurveda places considerable emphasis on hair care, with techniques such as Murdhni Thaila, the therapeutic oiling of the scalp. Hair care held importance across ancient cultures: in the Middle East and India, Bakhoor—a fragrant blend of aromatic woods, resins, and spices—was burned to gently perfume and dry the hair. During China's Han Dynasty, the government mandated a communal bath and hair-washing day every fifth day. People used rice water for hair and scalp care, beneficial also for dry skin, alongside plant ash and other natural agents.[13,14]

While these traditional practices reflect a long-standing cultural preoccupation with skin and hair health, modern dermatological research reveals a complex picture, particularly in conditions like hidradenitis suppurativa (HS), where inflammation at the hair follicle intersects with systemic disease. HS is a chronic inflammatory skin condition with distinct skin changes, and a spectrum of comorbidities including metabolic, cardiovascular, musculoskeletal, gastrointestinal, and mood disorders. Lesions form around terminal hair follicle units, with inflammatory nodules persisting in intertriginous zones and potentially evolving into branched, epithelized tunnels over time [56]. The autoinflammatory syndrome is driven by genetic, environmental, and behavioral factors.[15]

Given overlapping inflammatory and neuropsychological pathways, Gau et al. conducted the first study examining the association between incident migraine and HS. Their multicenter cohort study found an elevated migraine risk in HS patients, particularly women, compared to other inflammatory dermatoses. Prior research had only explored prevalent migraine in HS patients. Chronic pain and the social stigma accompanying HS may contribute to psychological stress, offering a potential link to increased migraine susceptibility [57].

2.3.5. *… To scalp: comorbidities in hidradenitis suppurativa*

In a second article featured in this issue of the *Biomedical Journal*, Gau et al. expand on their investigation into the systemic implications of hidradenitis suppurativa (HS), this time examining its association with alopecia areata (AA). AA is an autoimmune condition marked by transient, non-scarring hair loss, with the hair follicle itself remaining intact. A key mechanism implicated in AA is the collapse of immune privilege at the hair follicle [58].

Given the shared inflammatory pathways between HS and AA, Gau et al. evaluated the risk of incident AA in individuals with HS. Drawing on data spanning a 15-year follow-up period, their findings indicate an elevated risk of AA among HS patients. A potentially increased susceptibility in female patients was observed, although this may reflect demographic imbalances within the study cohort rather than a true sex-specific effect.

The authors suggest that the chronic inflammatory environment in HS contributes to the development of comorbidities across multiple organ systems. Their findings add to the emerging evidence pointing to a long-term association between HS and autoimmune-mediated hair loss [59].

[11] https://pubchem.ncbi.nlm.nih.gov/compound/Xanthine, last access 05/11/2025.

[12] https://www.ncbi.nlm.nih.gov/books/NBK559096/, last access 05/11/2025.

[13] https://thehistorianshut.com/2018/11/10/ancient-chinese-han-officials-loved-bath-and-hair-washing-day/, last access 05/08/2025.

[14] https://www.thenanjinger.com/magazine/feature-stories/maintaining-personal-hygiene-in-ancient-china/, last access 05/08/2025.

[15] https://www.ncbi.nlm.nih.gov/books/NBK534867/, last access 05/08/2025.

2.4. Letter to editor

2.4.1. Red alerts

In their correspondence, Bjørklund et al. critically examine a prior report by Dima et al. on the potential effects of the SARS-CoV-2 spike protein on erythrocyte biology. The original study had proposed that red blood cell morphology may be compromised upon exposure to SARS-CoV-2 spike proteins [60].

Bjørklund et al. raise concerns regarding the lack of specificity in the description of the spike protein variant used, as well as the absence of appropriate controls to rule out non-specific protein effects [61].

2.4.2. On SARS-CoV-2 spike proteins and erythrocyte morphology

In response to the critique by Bjørklund et al., Dima, Salvagno, and Lippi take the opportunity to clarify methodological details. They note that sourcing information for the SARS-CoV-2 spike protein was omitted due to space limitations and now provide this information explicitly. Additionally, they address remaining uncertainties, including ambiguity surrounding the reported protein concentrations, which they attribute to linguistic nuances. The authors maintain that inclusion of additional protein controls is not warranted, citing alignment with standard practices in comparable experimental studies [62].

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT Open AI in order to improve readability and language of the work. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing intersr

The author declares no conflict of interests.

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None.

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