Applied Microbiology and Biotechnology (2025) 109:218
https://doi.org/10.1007/s00253-025-13570-7

MINI REVIEW

Bidirectional interactions between circadian rhythms and the gut microbiome

Jhommara Bautista[1,2] · Sofía Ojeda-Mosquera[1] · Adriana Altamirano-Colina[1] · Camila Hidalgo-Tinoco[1] · Miranda Di Capua Delgado[1] · Andrés López-Cortés[1]

Received: 17 April 2025 / Revised: 29 July 2025 / Accepted: 31 July 2025

Abstract

Circadian rhythms are endogenous, near-24-h cycles that synchronize physiological and behavioral functions with environmental cues such as light/dark cycles and food intake. While the central pacemaker in the suprachiasmatic nucleus orchestrates these rhythms, peripheral clocks distributed across organs, including the gastrointestinal tract, exhibit autonomous oscillations that are crucial for local homeostasis. Concurrently, the gut microbiota undergoes diurnal fluctuations in composition and metabolic activity that are tightly coupled to host circadian mechanisms. Recent discoveries reveal a bidirectional relationship: host clocks influence microbial dynamics through feeding behavior, immune signaling, and epithelial renewal, whereas microbial metabolites such as short-chain fatty acids (SCFAs) and bile acids modulate circadian gene expression in peripheral tissues. Disruptions in circadian alignment, whether due to genetic mutations, lifestyle factors like shift work and irregular eating, or environmental perturbations, lead to microbial dysbiosis, metabolic dysfunction, inflammation, and heightened disease susceptibility. Conversely, altered microbiota rhythms can feed back into host systems, impairing metabolic control, immune responses, and neuroendocrine signaling. This reciprocal regulation extends to disease contexts, where circadian-microbiota misalignment contributes to obesity, type 2 diabetes, inflammatory bowel disease, and even neuropsychiatric disorders. This review synthesizes current insights into the molecular and physiological cross-talk between host circadian clocks and the gut microbiota. We discuss how temporal dynamics at the cellular, systemic, and microbial levels are integrated and how their disruption underlies pathogenesis. We further explore the potential of chronobiotics and chrononutrition, including time-restricted feeding (TRF) and bioactive dietary compounds, as emerging strategies to restore circadian-microbial synchrony and improve metabolic health. Understanding this intricate dialogue between host and microbiome may pave the way for personalized, time-based interventions to enhance healthspan and prevent disease occurrence or progression.

Key points

- *Circadian rhythms and microbiota form a bidirectional regulatory feedback loop.*
- *Disruption of circadian-microbial synchrony drives metabolic and inflammatory disease.*
- *Chrononutrition offers novel strategies to restore health via circadian–microbiota alignment.*

Keywords Circadian rhythms · Peripheral clocks · Gut microbiota · Dysbiosis · Chrononutrition

Introduction

Circadian rhythms are endogenous, near-24-h oscillations that coordinate a wide range of physiological and behavioral processes in alignment with environmental cycles such as light and feeding. These rhythms are maintained by a hierarchical network of molecular clocks, with the central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks present in nearly all tissues, including the gastrointestinal tract (Zhao et al.

✉ Andrés López-Cortés
aalc84@gmail.com

[1] Cancer Research Group (CRG), Faculty of Medicine, Universidad de Las Américas, Quito, Ecuador

[2] Facultade de Ciencias, Campus de A Zapateira, Universidade da Coruña, A Coruña, Spain

Published online: 10 October 2025

2022). Increasing evidence has revealed that not only host tissues, but also the gut microbiota, the diverse community of microorganisms residing in the digestive tract, undergoing rhythmic fluctuations that are tightly coupled with circadian mechanisms (Lotti et al. 2023; Schmalle and Lorentz 2020).

The gut microbiota plays a fundamental role in host homeostasis, contributing to digestion, immune regulation, and metabolic balance. It is now recognized that this microbial ecosystem exhibits its diurnal patterns in terms of composition, function, and metabolite production (Rowland et al. 2018). These microbial oscillations are influenced by host circadian rhythms and feeding behaviors, but also reciprocally modulate host clocks through microbial-derived signals such as short-chain fatty acids (SCFAs) and bile acids (Schmalle and Lorentz 2020; Thaiss et al. 2014). This bidirectional interaction establishes a finely tuned dialogue between the host's internal timekeeping systems and the microbial environment.

Disruptions to circadian rhythms, whether genetic or environmentally induced, can lead to microbial dysbiosis, characterized by loss of rhythmicity, altered community structure, and impaired microbial functions. Such alterations are implicated in the pathogenesis of various diseases, including obesity, type 2 diabetes, inflammatory bowel disease, and even cancer (Altaha et al. 2022; Yang et al. 2025; Zhao et al. 2022). Conversely, changes in microbiota composition or activity can impair host circadian gene expression and metabolic regulation, suggesting that microbial signals may serve as both effectors and modulators of circadian physiology (Bishehsari et al. 2016; Thaiss et al. 2014).

Modern lifestyles, particularly those involving shift work, irregular eating patterns, and artificial light exposure, are major contributors to circadian disruption and have been linked to metabolic and inflammatory diseases (El-Tanani et al. 2024). These lifestyle-induced changes are often accompanied by concurrent disturbances in the gut microbiota, further reinforcing the need to understand the crosstalk between these systems (Lotti et al. 2023; Yang et al. 2025).

This review aims to synthesize recent advances in our understanding of the interactions between circadian rhythms and the gut microbiome. We explore how these dynamic systems influence each other at molecular, cellular, and systemic levels, and examine their joint roles in health maintenance and disease development. Special attention is given to dietary timing, microbial metabolites, and potential chronotherapeutic strategies targeting the microbiota-circadian axis.

Circadian rhythms: a brief overview

The approximately 24-h cycles of circadian rhythms regulate a wide range of physiological, metabolic, and behavioral processes, enabling organisms to adapt to daily environmental fluctuations (Fagiani et al. 2022). These rhythms are orchestrated by a hierarchically organized circadian system, with a central pacemaker located in the SCN of the hypothalamus and autonomous peripheral clocks distributed across virtually all tissues, including the gastrointestinal tract (Bishehsari et al. 2016; Gutierrez Lopez et al. 2021; Heddes et al. 2022).

At the molecular level, the circadian system is driven by a set of highly conserved clock genes that interact through interlocking transcriptional–translational feedback loops (TTFLs). The core positive elements, *CLOCK* and *BMAL1*, activate the transcription of negative regulators such as *PER1/2/3* and *CRY1/2* (Pérez-Villa et al. 2023). These repressor proteins eventually inhibit CLOCK:BMAL1 heterodimer activity, generating rhythmic expression of numerous downstream clock-controlled genes (CCGs). Ancillary regulators, including *REV-ERBs* and *RORs*, provide additional layers of modulation, ensuring precision and robustness of the circadian oscillations (Heddes et al. 2022; Malloy et al. 2012).

While the central clock is primarily entrained by light signals received through the retinohypothalamic tract, peripheral clocks can also be synchronized by non-photic cues such as feeding schedules, temperature, hormones, and physical activity (Begemann et al. 2025; Leone et al. 2022). Notably, the gastrointestinal clock is sensitive to food intake patterns, and feeding rhythms are sufficient to entrain local circadian gene expression even in the absence of central cues (Altaha et al. 2022; Liang et al. 2015; Malloy et al. 2012). Additionally, Greenwell et al. have shown that more than 70% of the cycling mouse liver transcriptome loses rhythmicity under arrhythmic feeding (Greenwell et al. 2019).

Disruption of circadian alignment, whether due to genetic mutations, shift work, or irregular eating habits, can desynchronize peripheral clocks from the central pacemaker. This misalignment has been associated with numerous adverse outcomes, including metabolic dysfunction, obesity, gastrointestinal disorders, and inflammation (Altaha et al. 2022; Liang et al. 2015; Pérez-Villa et al. 2023). For example, mice lacking functional *BMAL1* or *PER* genes exhibit altered glucose metabolism, increased adiposity, and impaired intestinal barrier function. Moreover, circadian disruption is known to affect the rhythmicity and functionality of the gut microbiota, further exacerbating host physiological imbalances (Malloy et al. 2012; Yang et al. 2025). Thus, understanding the mechanistic basis of circadian regulation and its synchronization across bodily systems is fundamental to elucidating how temporal organization influences health. In the context of the gut microbiome, this rhythmic framework provides critical insight into host-microbe interactions, metabolic programming, and potential avenues for chronobiotic interventions.

Peripheral clocks in organs are not merely passive followers of the central SCN clock but are actively involved in maintaining tissue-specific homeostasis (Bautista et al. 2025b). In the intestine, the local clock regulates epithelial renewal and antimicrobial peptide production, thereby shaping microbial community structure (Heddes et al. 2022). In the liver, microbial metabolites such as SCFAs and bile acids entrain circadian transcription via peroxisome proliferator-activated receptor gamma (PPARγ) and FXR signaling, influencing metabolic programming (Murakami et al. 2016). These findings underscore the mechanistic role of peripheral clocks as both sensors and effectors of microbiota-derived cues.

The dynamic gut microbiota and its rhythmicity

The human gastrointestinal tract hosts a highly diverse and metabolically active microbial ecosystem, composed of bacteria, archaea, fungi, viruses, and protists. This microbial community, often referred to as the gut microbiota, performs essential functions for the host, including fermentation of indigestible dietary fibers, vitamin synthesis, xenobiotic metabolism, and modulation of immune and neuroendocrine systems (Hou et al. 2022; Liang and FitzGerald 2017). Among these organisms, bacteria are the most abundant and well-characterized, with the phyla *Bacillota* and *Bacteroidota* dominating in both human and murine models (Arumugam et al. 2011; Liang and FitzGerald 2017).

Traditionally perceived as relatively stable in adulthood, the gut microbiota is now recognized to exhibit robust diurnal oscillations in composition, localization, and functional activity. These fluctuations are not random but rather governed by both endogenous circadian mechanisms and external cues such as feeding schedules and nutrient composition (Heddes et al. 2022; Zhang et al. 2023; Y. Zhang et al. 2024a, b). Approximately 10–15% of microbial taxa undergo time-of-day-dependent changes in abundance and gene expression patterns, with specific taxa peaking during feeding or fasting phases, depending on host behavior and environmental context (Heddes et al. 2022; Liang et al. 2015).

Several microbial taxa exhibit robust circadian oscillations in abundance and function. For instance, members of the *Bacteroides*, *Lactobacillus*, and *Clostridiales* genera peak during specific phases of feeding-fasting cycles (Liang et al. 2015; Thaiss et al. 2014). These rhythmic taxa contribute to SCFA production, bile acid conversion, and epithelial barrier integrity. Disruption of these oscillations, via altered feeding or circadian misalignment, leads to reduced metabolic efficiency and heightened inflammatory tone (dos Santos and Vasylyshyn 2025; Ferrell and Chiang 2015).

At the functional level, microbial activities, including fermentation, flagellar assembly, and bile acid transformation, also oscillate across the day–night cycle. For instance, SCFAs, which serve as energy sources and immune modulators, exhibit circadian patterns in their production, often aligning with host feeding times and gut motility rhythms (Liang et al. 2015; Zhang et al. 2023). Notably, such microbial rhythmicity is tightly coupled with host circadian clocks. Disruption of CCGs in mice is associated with a loss of microbial rhythmicity, alterations in community composition, and metabolic impairments such as glucose intolerance and increased adiposity, although the directionality of these effects remains under investigation (Altaha et al. 2022; Liang et al. 2015).

The interplay between feeding rhythms and microbial cycles is particularly evident in time-restricted feeding (TRF) paradigms. Imposing TRF restores microbial rhythmicity in clock-deficient mice and enhances metabolic health, highlighting a powerful role of feeding time in entraining microbiota function independently of the central clock (Zeb et al. 2021; Zhang et al. 2023; Y. Zhang et al. 2024a, b). Furthermore, the microbiota itself influences host rhythms by modulating gene expression in peripheral tissues such as the liver and intestine, partly through microbial metabolites and epigenetic remodeling of host chromatin (Montagner et al. 2016; Murakami et al. 2016; Y. Zhang et al. 2024a, b).

Interestingly, although the microbiome contributes to enhancing the amplitude and precision of circadian rhythms in some contexts, it may also buffer excessive fluctuations in gene expression under environmental perturbations, thereby maintaining circadian synchrony across tissues (Zhang et al. 2023; Y. Zhang et al. 2024a, b). This bidirectional regulation underscores the gut microbiota's role as both a target and regulator of the host circadian system. Altogether, the dynamic nature of the gut microbiota, its intrinsic rhythmicity and responsiveness to host and environmental cues, adds a complex and adaptive layer to the regulation of metabolic and immune homeostasis.

Cross-talk between circadian clocks and gut microbiota

The relationship between host circadian clocks and the gut microbiota is fundamentally bidirectional, forming a dynamic interplay that is essential for maintaining physiological homeostasis (Fig. 1). On one hand, circadian clocks regulate the composition, localization, and metabolic activity of the microbiota; on the other hand, microbial-derived signals can entrain or modulate circadian rhythms in peripheral tissues (Lotti et al. 2023; Zhao et al. 2022).

At the host level, circadian rhythms are governed by a hierarchical clock system. The central pacemaker in the SCN synchronizes peripheral clocks through light-dependent signaling. However, feeding behavior, hormonal secretion,

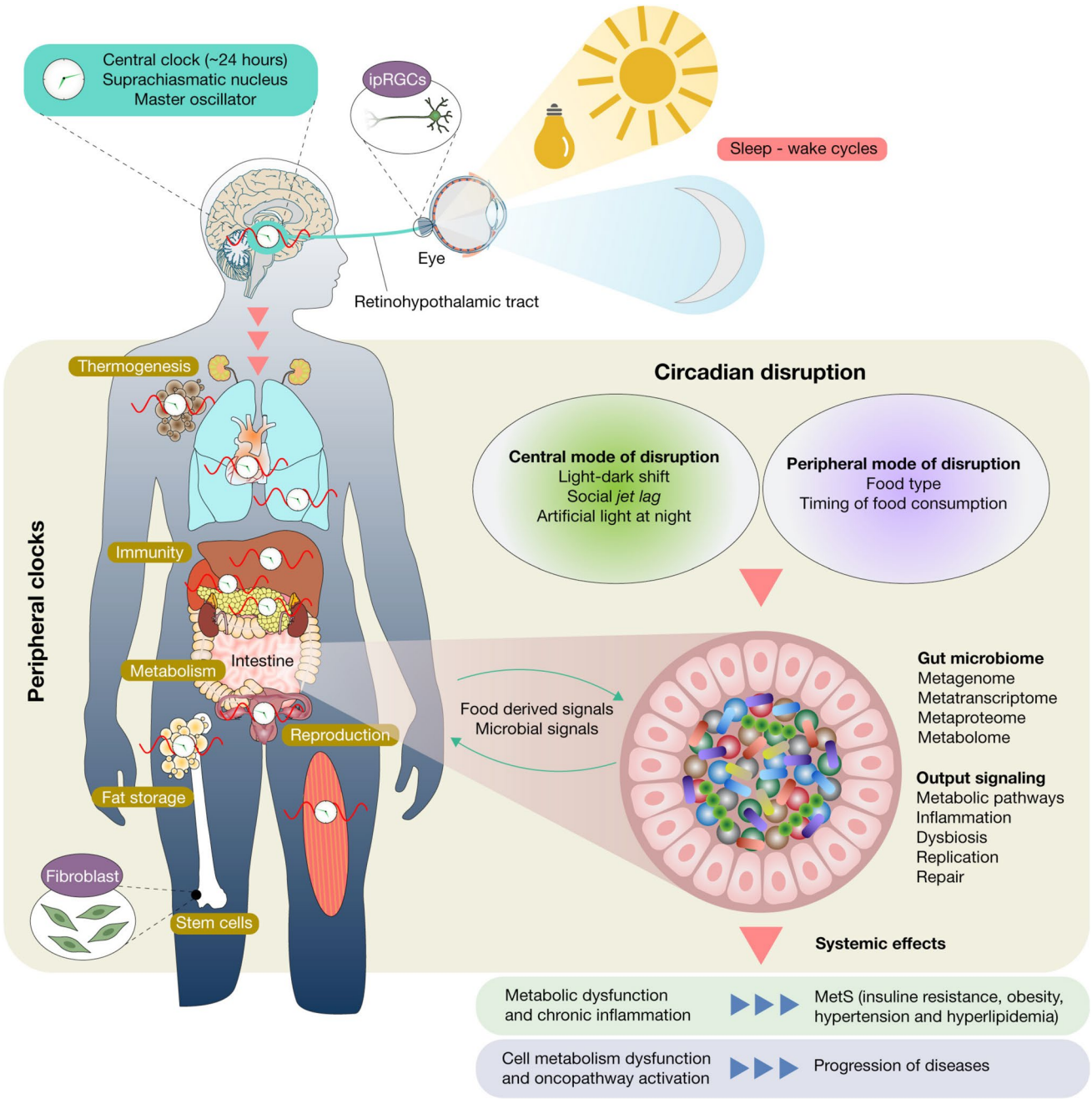

Fig. 1 Cross-talk between circadian rhythms, peripheral clocks, and the gut microbiome. This figure illustrates the dynamic and reciprocal interactions between host circadian rhythms and the gut microbiome. Peripheral clocks synchronize with central rhythms and are influenced by microbial-derived signals. In turn, circadian cues shape microbial composition and function. Disruptions in this bidirectional dialogue can lead to circadian misalignment and contribute to the development and progression of metabolic, inflammatory, and neoplastic diseases

and local tissue factors also act as potent *zeitgebers* for peripheral tissues such as the gut. These peripheral clocks exhibit autonomous rhythmicity but are also entrainable by microbial signals and dietary patterns (Heddes et al. 2022; Zhao et al. 2022). Intestinal epithelial clocks have been shown to orchestrate microbiota diurnal oscillations, particularly through regulation of antimicrobial peptide secretion, epithelial renewal, and nutrient availability (Heddes et al. 2022).

The gut microbiota exhibits distinct temporal organization, with oscillations in both taxonomic abundance and functional output, such as the production of SCFAs, bile

acids, and microbial metabolites (Choi et al. 2021). These microbial rhythms are heavily influenced by the host's feeding cycles and circadian machinery. Loss of rhythmicity in microbial communities has been observed in both genetic models of circadian disruption and under environmental misalignment, such as simulated shift work. These alterations are linked to metabolic consequences, including glucose intolerance, increased adiposity, and low-grade inflammation (Lotti et al. 2023; Zhang et al. 2023).

In turn, microbial metabolites act as entraining agents or modulators of host clocks. SCFAs like butyrate and propionate have been shown to influence peripheral clock gene expression, while secondary bile acids and methionine derivatives from microbes affect nuclear receptor signaling and oxidative stress responses in host tissues (Liu et al. 2023; Schmalle and Lorentz 2020). Initial findings demonstrated that microbial communities can reprogram hepatic circadian transcription through PPARγ signaling (Murakami et al. 2016), a concept further supported by more recent multi-omic analyses (Huang et al. 2023).

TRF, when aligned with the circadian cycle, has been shown to restore microbial rhythmicity and improve host metabolic and immune outcomes in models of circadian disruption. Conversely, circadian misalignment induced by high-fat diets, irregular feeding schedules, or simulated jet lag disrupts microbial oscillations and exacerbates host clock desynchrony, creating a pathological feedback loop (Thaiss et al. 2014; Y. Zhang et al. 2024a, b). These findings underscore the importance of feeding timing in synchronizing host–microbiota interactions and maintaining physiological homeostasis.

Germ-free mouse models further underscore the essential role of the microbiome in regulating host circadian physiology. These mice display impaired locomotor activity rhythms, altered core body temperature cycles, and diminished amplitude of peripheral clock gene expression (Leone et al. 2022; Zhang et al. 2025). Fecal microbiota transplantation (FMT) from jet-lagged or high-fat-diet-fed donors induces circadian misalignment and metabolic disturbances in recipients (Thaiss et al. 2014). Conversely, microbial transfer from healthy donors can restore rhythmic gene expression in hepatic tissues through PPARγ signaling, emphasizing the causal role of microbial oscillations in synchronizing host clocks (Murakami et al. 2016).

Importantly, recent studies have clarified the role of peripheral clocks in disease susceptibility. Loss of the intestinal epithelial clock alone does not trigger gastrointestinal pathology under basal conditions, but significantly aggravates inflammation and mortality in IL-10-deficient and DSS-induced colitis models, demonstrating its essential role in microbial rhythmicity and mucosal immune regulation (Niu et al. 2024). Likewise, the liver clock does not directly entrain other peripheral clocks, but it strongly modulates their transcriptional rhythmicity in response to feeding. Liver-specific Bmal1 deficiency alters the rhythmic transcriptome of distal organs such as white adipose tissue and lung without disrupting their core clock oscillations, indicating that the liver clock acts as a systemic buffer against nutritional perturbations (Manella et al. 2021) These findings reveal that peripheral clocks are not merely passive recipients of SCN cues, but rather play active and tissue-specific roles in disease modulation and systemic homeostasis. Overall, this cross-talk constitutes a complex feedback loop whereby the circadian system not only regulates microbial dynamics but is also reciprocally shaped by microbiota-derived signals.

Chronobiotics in chrononutrition

Chrononutrition is an emerging field that emphasizes the alignment of dietary intake with the body's internal circadian clock. It encompasses not only the type and quantity of food consumed but also its timing and frequency, which are critical for maintaining metabolic homeostasis. Within this framework, *chronobiotics* refer to bioactive compounds or interventions, often derived from food, that are capable of modulating circadian rhythms by either reinforcing or shifting the phase of internal clocks (Dufoo-Hurtado et al. 2020; X.-Y. Zhang et al. 2024a, b).

Recent findings suggest that melatonin not only modulates circadian rhythms but also interacts intimately with the intestinal microbiome, creating a bidirectional relationship relevant to chrononutrition (Iesanu et al. 2022). Gut microbes and their metabolites can stimulate intestinal melatonin production, while melatonin, in turn, shapes microbial composition and activity. Notably, melatonin is synthesized not only in the pineal gland but also by intestinal enterochromaffin cells and even certain microbial taxa, highlighting the gastrointestinal tract as both a source and target of melatonin-mediated signaling (Zimmermann et al. 2024). This interconnection has implications for systemic circadian regulation, metabolic homeostasis, and gut health, positioning microbial–melatonin cross-talk as a novel therapeutic axis for rhythm-associated disorders.

The rationale behind chrononutrition stems from the observation that both the central and peripheral clocks, including those in the gastrointestinal tract, are highly responsive to meal timing. Nutrient intake acts as a potent *zeitgeber*, or time cue, particularly for peripheral clocks that are sensitive to metabolic inputs. Disruptions in feeding rhythms, such as breakfast skipping, late-night eating, or irregular meal schedules, have been associated with circadian misalignment and increased risk of metabolic diseases, including obesity, type 2 diabetes, and cardiovascular disorders (Boege et al. 2021; Saidi et al. 2024).

Chronobiotics may help mitigate these disruptions by entraining or resynchronizing desynchronized clocks (Greenwell et al. 2019). Among the most studied natural chronobiotics are melatonin, caffeine, and tryptophan-rich foods, which influence clock gene expression and sleep–wake cycles through their interactions with molecular oscillators and neuroendocrine pathways (Cardinali et al. 2006; Dufoo-Hurtado et al. 2020). For example, melatonin, commonly derived from plant sources such as tart cherries or tomatoes, has been shown to regulate circadian amplitude and phase, improving both sleep quality and metabolic markers (Dufoo-Hurtado et al. 2020; Kent et al. 2022). Similarly, caffeine can delay circadian phase by acting on adenosine receptors and modulating intracellular cAMP levels, which influence core clock gene expression.

Beyond metabolic effects, recent evidence highlights the role of TRF in modulating intestinal inflammation through peripheral clock–microbiota crosstalk. Niu et al. showed that TRF during the active phase ameliorated colitis symptoms in IL-10$^{-/-}$ ice by enhancing epithelial regeneration and modulating microbiota composition (Niu et al. 2024). However, these protective effects were abolished in mice lacking the intestinal epithelial clock gene *Bmal1*, despite partial restoration of microbial richness. This indicates that TRF-driven improvements in microbiota require a functional intestinal circadian clock to translate into anti-inflammatory outcomes, emphasizing the interdependence between microbial rhythmicity, peripheral clocks, and disease modulation (Zhai et al. 2025).

Additionally, the microbiota appears to play a critical role in mediating melatonin's therapeutic benefits in extra-circadian contexts, including cognitive function. A recent study demonstrated that the beneficial effects of melatonin on memory and neuroinflammation were abolished in microbiota-depleted mice, indicating that microbial presence is essential for melatonin's neuroprotective effects (Wang et al. 2023). This suggests that melatonin–microbiota interactions extend beyond local gut effects, potentially modulating gut–brain communication and contributing to chronobiotic actions in systemic disease settings (Bautista et al. 2025a).

Despite promising preclinical findings, clinical research on the chronobiotic properties of specific dietary compounds remains limited. Most studies focus on single nutrients or controlled feeding schedules, making it difficult to generalize to real-life dietary behaviors (Lee et al. 2022). Additionally, individual chronotypes, microbiota profiles, and metabolic phenotypes likely influence the efficacy of chrononutritional interventions, suggesting a need for personalized approaches (Dufoo-Hurtado et al. 2020; Saidi et al. 2024). Chronobiotics represent a promising strategy to leverage diet as a modulator of circadian health. Through targeted timing of nutrient intake and incorporation of bioactive compounds with clock-modulating properties, chrononutrition may offer novel therapeutic avenues to combat circadian misalignment and its associated metabolic consequences.

Gut microbiota and circadian rhythms in disease

Disruptions in circadian rhythms and gut microbiota homeostasis are increasingly recognized as co-contributors to a broad spectrum of diseases, particularly metabolic, gastrointestinal, cardiovascular, and neuropsychiatric disorders (Codoñer-Franch et al. 2023; Hayter et al. 2021; Rijo-Ferreira and Takahashi 2019; Zhao et al. 2022). These systems are intimately linked; perturbations in one often lead to dysfunction in the other, creating a self-reinforcing cycle that exacerbates disease risk and severity (Bishehsari et al. 2020; Li et al. 2018).

Modern lifestyle factors, such as shift work, frequent time zone travel, erratic sleep patterns, and irregular feeding schedules, profoundly impact circadian alignment. These environmental and behavioral disruptions result in desynchronization of peripheral clocks and altered microbial rhythmicity, a phenomenon termed circadian dysrhythmia (Bishehsari et al. 2020; Gutierrez Lopez et al. 2021). In metabolic contexts, this misalignment impairs glucose homeostasis, promotes insulin resistance, and increases adiposity. For instance, both genetic (e.g., *BMAL1* deficiency) and environmental models of circadian disruption result in reduced oscillatory behavior of microbiota taxa critical for short-chain fatty acid production and lipid metabolism, linking microbial desynchronization to the development of obesity and type 2 diabetes (Altaha et al. 2022; Fan and Pedersen 2021; Kohsaka et al. 2007). A recent large-scale human cohort study further supported this link, showing that individuals with arrhythmic gut microbial signatures had a significantly higher risk of developing type 2 diabetes over four years (Reitmeier et al. 2020).

Beyond metabolic diseases, gut microbiota–circadian interactions are implicated in gastrointestinal inflammation and barrier dysfunction. Circadian misalignment exacerbates intestinal permeability and shifts microbiota toward pro-inflammatory profiles. In inflammatory bowel disease, reductions in beneficial microbes such as *F. prausnitzii*, *Akkermansia muciniphila*, and *Bifidobacterium* have been consistently observed alongside increased rhythmicity loss and mucosal immune activation (Bishehsari et al. 2016). These changes contribute to chronic intestinal inflammation and epithelial damage.

Neuropsychiatric conditions, including insomnia and depression, are also linked to circadian–microbiota dysregulation (Jiang et al. 2022). Through the gut-brain axis, the microbiome influences neuroendocrine signaling, glucocorticoid rhythms, and neurotransmitter availability, all of which are under circadian control. Disruption of microbial rhythmicity affects stress responsivity via the

hypothalamic–pituitary–adrenal (HPA) axis, contributing to affective and sleep disorders (Li et al. 2018; Teichman et al. 2020; Tofani et al. 2025). Experimental evidence indicates that microbial depletion alters the diurnal secretion of corticosterone and modulates stress-sensitive brain regions such as the hippocampus and amygdala (Tofani et al. 2025).

Mechanistically, gut microbes influence host disease processes through metabolites that interact with nuclear receptors and signaling pathways controlling circadian and metabolic homeostasis. For example, microbial modulation of PPARγ activity can reprogram hepatic circadian transcription in response to dietary challenges, linking microbial dysbiosis to liver metabolic dysfunction (Murakami et al. 2016). Collectively, these findings underscore the critical role of gut microbiota–circadian cross-talk in health and disease. Disruptions to this axis contribute to disease pathogenesis through metabolic deregulation, inflammation, impaired barrier function, and altered neuroendocrine signaling.

Conclusions and future perspectives

The interaction between circadian rhythms and the gut microbiota represents a vital axis that underpins host metabolic, immunologic, and neuroendocrine homeostasis. Mounting evidence suggests that these systems are reciprocally regulated: the host circadian clock shapes microbial oscillations, while microbial metabolites modulate circadian gene expression in peripheral tissues (Bishehsari et al. 2020; Gutierrez Lopez et al. 2021; Murakami et al. 2016). Disruption of this finely tuned dialogue, via genetic alterations, environmental misalignment, or lifestyle-induced chronodisruption, leads to a cascade of pathological consequences, including metabolic syndrome, inflammatory bowel diseases, and neuropsychiatric disorders (Altaha et al. 2022; Li et al. 2018).

Advances in high-resolution temporal profiling, germ-free animal models, and multi-omics technologies have revealed critical mechanisms by which microbial rhythms and circadian clocks are synchronized. For example, feeding rhythms, short-chain fatty acid production, bile acid metabolism, and microbial regulation of nuclear receptors such as PPARγ and REV-ERBα all contribute to the entrainment and functional outputs of host circadian pathways (Bishehsari et al. 2020; Murakami et al. 2016; Tahara et al. 2018; Thaiss et al. 2014). The desynchronization of these interactions not only alters microbial diversity and function but also drives host metabolic dysfunction, intestinal barrier breakdown, and systemic inflammation (Altaha et al. 2022; Bishehsari et al. 2016).

Future research should focus on identifying specific microbial taxa and metabolites that exert chronobiotic effects, as well as deciphering host genetic and epigenetic regulators that mediate microbial influence on circadian physiology (Gutierrez Lopez et al. 2021; Pérez-Villa et al. 2023; Thaiss et al. 2014). Precision chrononutrition and microbial-targeted interventions, such as probiotics, prebiotics, postbiotics, and TRF, offer exciting avenues for restoring rhythmic homeostasis in disease contexts (Gutierrez Lopez et al. 2021; Srivastava et al. 2021; Tofani et al. 2025). Moreover, emerging evidence supports the application of circadian principles in therapeutic scheduling (chronotherapy), particularly in the management of metabolic diseases and cancer, where the timing of drug delivery or nutrient intake may influence efficacy and toxicity (Fan and Pedersen 2021; Pérez-Villa et al. 2023).

Ultimately, integrating circadian biology with microbiome science holds promise for developing personalized, time-based medical strategies aimed at improving healthspan and preventing disease. A systems-level understanding of the temporal orchestration between host and microbiota will be essential for translating these discoveries into clinically actionable interventions (Bishehsari et al. 2020; Fan and Pedersen 2021; Gutierrez Lopez et al. 2021).

Acknowledgements This work was supported by Universidad de Las Américas (UDLA) from Quito, Ecuador.

Author contributions J.B. and A.L.C. conceived the subject and the conceptualization of the study. J.B., S.O.M., A.A.C., C.H.T., and M.D.D. did data curation. J.B., S.O.M., A.A.C., C.H.T., and M.D.D. gave conceptual advice and valuable scientific input. A.L.C. supervised and did funding acquisition. Finally, all authors wrote, reviewed, and approved the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This article does not contain any studies with human participants performed by any of the authors.

Competing interests The authors declare no competing interests.

References

Altaha B, Heddes M, Pilorz V, Niu Y, Gorbunova E, Gigl M, Kleigrewe K, Oster H, Haller D, Kiessling S (2022) Genetic and environmental circadian disruption induce weight gain through changes in the gut microbiome. Mol Metab 66:101628. https://doi.org/10.1016/j.molmet.2022.101628

Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto J-M, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Bork P (2011) Enterotypes of the human gut microbiome. Nature 473:174–180. https://doi.org/10.1038/nature09944

Bautista J, Ávila-Coello D, Hidalgo-Tinoco C, Bueno-Miño J, López-Cortés A (2025) Unraveling the gut-brain-immune interplay in herpes simplex virus-associated neurodegeneration. J Med Virol 97:e70504. https://doi.org/10.1002/jmv.70504

Bautista J, Ojeda-Mosquera S, Ordóñez-Lozada D, López-Cortés A (2025) Peripheral clocks and systemic zeitgeber interactions: from molecular mechanisms to circadian precision medicine. Front Endocrinol (Lausanne) 16:1606242. https://doi.org/10.3389/fendo.2025.1606242

Begemann K, Rawashdeh O, Olejniczak I, Pilorz V, de Assis LVM, Osorio-Mendoza J, Oster H (2025) Endocrine regulation of circadian rhythms. NPJ Biol Timing Sleep 2:10. https://doi.org/10.1038/s44323-025-00024-6

Bishehsari F, Levi F, Turek FW, Keshavarzian A (2016) Circadian rhythms in gastrointestinal health and diseases. Gastroenterology 151:e1-5. https://doi.org/10.1053/j.gastro.2016.07.036

Bishehsari F, Voigt RM, Keshavarzian A (2020) Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer. Nat Rev Endocrinol 16:731–739. https://doi.org/10.1038/s41574-020-00427-4

Boege HL, Bhatti MZ, St-Onge M-P (2021) Circadian rhythms and meal timing: impact on energy balance and body weight. Curr Opin Biotechnol 70:1–6. https://doi.org/10.1016/j.copbio.2020.08.009

Cardinali DP, Furio AM, Reyes MP, Brusco LI (2006) The use of chronobiotics in the resynchronization of the sleep-wake cycle. Cancer Causes Control 17:601–609. https://doi.org/10.1007/s10552-005-9009-2

Choi H, Rao MC, Chang EB (2021) Gut microbiota as a transducer of dietary cues to regulate host circadian rhythms and metabolism. Nat Rev Gastroenterol Hepatol 18:679–689. https://doi.org/10.1038/s41575-021-00452-2

Codoñer-Franch P, Gombert M, Martínez-Raga J, Cenit MC (2023) Circadian disruption and mental health: the chronotherapeutic potential of microbiome-based and dietary strategies. Int J Mol Sci. https://doi.org/10.3390/ijms24087579

dos Santos A, Vasylyshyn A (2025) The modulatory role of short-chain fatty acids on peripheral circadian gene expression: a systematic review. Front Physiol. https://doi.org/10.3389/fphys.2025.1595057

Dufoo-Hurtado E, Wall-Medrano A, Campos-Vega R (2020) Naturally-derived chronobiotics in chrononutrition. Trends Food Sci Technol 95:173–182. https://doi.org/10.1016/j.tifs.2019.11.020

El-Tanani M, Rabbani SA, Ali AA, Alfaouri IGA, Al Nsairat H, Al-Ani IH, Aljabali AA, Rizzo M, Patoulias D, Khan MA, Parvez S, El-Tanani Y (2024) Circadian rhythms and cancer: implications for timing in therapy. Discover Oncol 15:767. https://doi.org/10.1007/s12672-024-01643-4

Fagiani F, Di Marino D, Romagnoli A, Travelli C, Voltan D, Di Cesare Mannelli L, Racchi M, Govoni S, Lanni C (2022) Molecular regulations of circadian rhythm and implications for physiology and diseases. Signal Transduct Target Ther 7:41. https://doi.org/10.1038/s41392-022-00899-y

Fan Y, Pedersen O (2021) Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 19:55–71. https://doi.org/10.1038/s41579-020-0433-9

Ferrell JM, Chiang JYL (2015) Short-term circadian disruption impairs bile acid and lipid homeostasis in mice. Cell Mol Gastroenterol Hepatol 1:664–677. https://doi.org/10.1016/j.jcmgh.2015.08.003

Greenwell BJ, Trott AJ, Beytebiere JR, Pao S, Bosley A, Beach E, Finegan P, Hernandez C, Menet JS (2019) Rhythmic food intake drives rhythmic gene expression more potently than the hepatic circadian clock in mice. Cell Rep 27:649-657.e5. https://doi.org/10.1016/j.celrep.2019.03.064

Gutierrez Lopez DE, Lashinger LM, Weinstock GM, Bray MS (2021) Circadian rhythms and the gut microbiome synchronize the host's metabolic response to diet. Cell Metab 33:873–887. https://doi.org/10.1016/j.cmet.2021.03.015

Hayter EA, Wehrens SMT, Van Dongen HPA, Stangherlin A, Gaddameedhi S, Crooks E, Barron NJ, Venetucci LA, O'Neill JS, Brown TM, Skene DJ, Trafford AW, Bechtold DA (2021) Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. Nat Commun 12:2472. https://doi.org/10.1038/s41467-021-22788-8

Heddes M, Altaha B, Niu Y, Reitmeier S, Kleigrewe K, Haller D, Kiessling S (2022) The intestinal clock drives the microbiome to maintain gastrointestinal homeostasis. Nat Commun 13:6068. https://doi.org/10.1038/s41467-022-33609-x

Hou K, Wu Z-X, Chen X-Y, Wang J-Q, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J, Chen Z-S (2022) Microbiota in health and diseases. Signal Transduct Target Ther 7:135. https://doi.org/10.1038/s41392-022-00974-4

Huang R, Chen J, Zhou M, Xin H, Lam SM, Jiang X, Li J, Deng F, Shui G, Zhang Z, Li M-D (2023) Multi-omics profiling reveals rhythmic liver function shaped by meal timing. Nat Commun 14:6086. https://doi.org/10.1038/s41467-023-41759-9

IesanuMI, Zahiu CDM, Dogaru I-A, Chitimus DM, Pircalabioru GG, Voiculescu SE, Isac S, Galos F, Pavel B, O'Mahony SM, Zagrean A-M (2022) Melatonin-microbiome two-sided interaction in dysbiosis-associated conditions. Antioxidants (Basel) 11. https://doi.org/10.3390/antiox11112244

Jiang Z, Zhuo L-B, He Y, Fu Y, Shen L, Xu F, Gou W, Miao Z, Shuai M, Liang Y, Xiao C, Liang X, Tian Y, Wang J, Tang J, Deng K, Zhou H, Chen Y-M, Zheng J-S (2022) The gut microbiota-bile acid axis links the positive association between chronic insomnia and cardiometabolic diseases. Nat Commun 13:3002. https://doi.org/10.1038/s41467-022-30712-x

Kent BA, Rahman SA, St Hilaire MA, Grant LK, Rüger M, Czeisler CA, Lockley SW (2022) Circadian lipid and hepatic protein rhythms shift with a phase response curve different than melatonin. Nat Commun 13:681. https://doi.org/10.1038/s41467-022-28308-6

Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J (2007) High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metab 6:414–421. https://doi.org/10.1016/j.cmet.2007.09.006

Lee BY, Ordovás JM, Parks EJ, Anderson CAM, Barabási A-L, Clinton SK, de la Haye K, Duffy VB, Franks PW, Ginexi EM, Hammond KJ, Hanlon EC, Hittle M, Ho E, Horn AL, Isaacson RS, Mabry PL, Malone S, Martin CK, Mattei J, Martinez MF (2022) Research gaps and opportunities in precision nutrition: an NIH workshop report. Am J Clin Nutr 116:1877–1900. https://doi.org/10.1093/ajcn/nqac237

Leone VA, Onishi KG, Kennedy M, Riggle JP, Pierre JF, Maneval AC, Spedale MN, Theriault BR, Chang EB, Prendergast BJ (2022) Atypical behavioral and thermoregulatory circadian rhythms in mice lacking a microbiome. Sci Rep 12:14491. https://doi.org/10.1038/s41598-022-18291-9

Li Y, Hao Y, Fan F, Zhang B (2018) The role of microbiome in insomnia, circadian disturbance and depression. Front Psychiatry 9:669. https://doi.org/10.3389/fpsyt.2018.00669

Liang X, FitzGerald GA (2017) Timing the microbes: the circadian rhythm of the gut microbiome. J Biol Rhythms 32:505–515. https://doi.org/10.1177/0748730417729066

Liang X, Bushman FD, FitzGerald GA (2015) Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. Proc Natl Acad Sci USA 112:10479–10484. https://doi.org/10.1073/pnas.1501305112

Liu X, Ma Y, Yu Y, Zhang W, Shi J, Zhang X, Dai M, Wang Y, Zhang H, Zhang J, Shen J, Zhang F, Song M, Wang J (2023) Gut microbial methionine impacts circadian clock gene expression and reactive oxygen species level in host gastrointestinal tract. Protein Cell 14:309–313. https://doi.org/10.1093/procel/pwac021

Lotti S, Dinu M, Colombini B, Amedei A, Sofi F (2023) Circadian rhythms, gut microbiota, and diet: possible implications for health. Nutr Metab Cardiovasc Dis 33:1490–1500. https://doi.org/10.1016/j.numecd.2023.05.009

Malloy JN, Paulose JK, Li Y, Cassone VM (2012) Circadian rhythms of gastrointestinal function are regulated by both central and peripheral oscillators. Am J Physiol Gastrointest Liver Physiol 303:G461–G473. https://doi.org/10.1152/ajpgi.00369.2011

Manella G, Sabath E, Aviram R, Dandavate V, Ezagouri S, Golik M, Adamovich Y, Asher G (2021) The liver-clock coordinates rhythmicity of peripheral tissues in response to feeding. Nat Metab 3:829–842. https://doi.org/10.1038/s42255-021-00395-7

Montagner A, Korecka A, Polizzi A, Lippi Y, Blum Y, Canlet C, Tremblay-Franco M, Gautier-Stein A, Burcelin R, Yen Y-C, Je HS, Al-Asmakh M, Mithieux G, Arulampalam V, Lagarrigue S, Guillou H, Pettersson S, Wahli W (2016) Hepatic circadian clock oscillators and nuclear receptors integrate microbiome-derived signals. Sci Rep 6:20127. https://doi.org/10.1038/srep20127

Murakami M, Tognini P, Liu Y, Eckel-Mahan KL, Baldi P, Sassone-Corsi P (2016) Gut microbiota directs PPARγ-driven reprogramming of the liver circadian clock by nutritional challenge. EMBO Rep 17:1292–1303. https://doi.org/10.15252/embr.201642463

Niu Y, Heddes M, Altaha B, Birkner M, Kleigrewe K, Meng C, Haller D, Kiessling S (2024) Targeting the intestinal circadian clock by meal timing ameliorates gastrointestinal inflammation. Cell Mol Immunol 21:842–855. https://doi.org/10.1038/s41423-024-01189-z

Pérez-Villa A, Echeverría-Garcés G, Ramos-Medina MJ, Prathap L, Martínez-López M, Ramírez-Sánchez D, García-Cárdenas JM, Armendáriz-Castillo I, Guerrero S, Paz C, López-Cortés A (2023) Integrated multi-omics analysis reveals the molecular interplay between circadian clocks and cancer pathogenesis. Sci Rep 13:14198. https://doi.org/10.1038/s41598-023-39401-1

Reitmeier S, Kiessling S, Clavel T, List M, Almeida EL, Ghosh TS, Neuhaus K, Grallert H, Linseisen J, Skurk T, Brandl B, Breuninger TA, Troll M, Rathmann W, Linkohr B, Hauner H, Laudes M, Franke A, Le Roy CI, Bell JT, Haller D (2020) Arrhythmic gut microbiome signatures predict risk of type 2 diabetes. Cell Host Microbe 28:258-272.e6. https://doi.org/10.1016/j.chom.2020.06.004

Rijo-Ferreira F, Takahashi JS (2019) Genomics of circadian rhythms in health and disease. Genome Med 11:82. https://doi.org/10.1186/s13073-019-0704-0

Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, Tuohy K (2018) Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr 57:1–24. https://doi.org/10.1007/s00394-017-1445-8

Saidi O, Rochette E, Dambel L, St-Onge M-P, Duché P (2024) Chrono-nutrition and sleep: lessons from the temporal feature of eating patterns in human studies - a systematic scoping review. Sleep Med Rev 76:101953. https://doi.org/10.1016/j.smrv.2024.101953

Schmalle V, Lorentz A (2020) Role of the microbiota in circadian rhythms of the host. Chronobiol Int 37:301–310. https://doi.org/10.1080/07420528.2020.1726374

Srivastava AK, Rohil V, Bhushan B, Eslavath MR, Gupta H, Chanda S, Kumar B, Varshney R, Ganju L (2021) Probiotics maintain the gut microbiome homeostasis during Indian Antarctic expedition by ship. Sci Rep 11:18793. https://doi.org/10.1038/s41598-021-97890-4

Tahara Y, Yamazaki M, Sukigara H, Motohashi H, Sasaki H, Miyakawa H, Haraguchi A, Ikeda Y, Fukuda S, Shibata S (2018) Gut microbiota-derived short chain fatty acids induce circadian clock entrainment in mouse peripheral tissue. Sci Rep 8:1395. https://doi.org/10.1038/s41598-018-19836-7

Teichman EM, O'Riordan KJ, Gahan CGM, Dinan TG, Cryan JF (2020) When rhythms meet the blues: circadian interactions with the microbiota-gut-brain axis. Cell Metab 31:448–471. https://doi.org/10.1016/j.cmet.2020.02.008

Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, Abramson L, Katz MN, Korem T, Zmora N, Kuperman Y, Biton I, Gilad S, Harmelin A, Shapiro H, Halpern Z, Segal E, Elinav E (2014) Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. Cell 159:514–529. https://doi.org/10.1016/j.cell.2014.09.048

Tofani GSS, Leigh S-J, Gheorghe CE, Bastiaanssen TFS, Wilmes L, Sen P, Clarke G, Cryan JF (2025) Gut microbiota regulates stress responsivity via the circadian system. Cell Metab 37:138-153.e5. https://doi.org/10.1016/j.cmet.2024.10.003

Wang X, Wang Z, Cao J, Dong Y, Chen Y (2023) Gut microbiota-derived metabolites mediate the neuroprotective effect of melatonin in cognitive impairment induced by sleep deprivation. Microbiome 11:17. https://doi.org/10.1186/s40168-022-01452-3

Yang Y, Hernandez MC, Chitre S, Jobin C (2025) Emerging roles of modern lifestyle factors in microbiome stability and functionality. Curr Clin Microbiol Rep 12:6. https://doi.org/10.1007/s40588-025-00242-3

Zeb F, Wu X, Feng Q (2021) Effect of time restricted feeding on metabolic risk and circadian rhythm associated with gut microbiome in healthy males. Curr Dev Nutr 5:476. https://doi.org/10.1093/cdn/nzab039_012

Zhai T, Zou X, Zhang Z, Wang Y, Shi L, Ren W, Huang J (2025) Circadian rhythms of gut microbiota and plaque vulnerability: mechanisms and chrono-microbiota modulation interventions. Gut Microbes 17:2532703. https://doi.org/10.1080/19490976.2025.2532703

Zhang Y, Li Y, Barber AF, Noya SB, Williams JA, Li F, Daniel SG, Bittinger K, Fang J, Sehgal A (2023) The microbiome stabilizes circadian rhythms in the gut. Proc Natl Acad Sci USA 120:e2217532120. https://doi.org/10.1073/pnas.2217532120

Zhang X-Y, Khakisahneh S, Han S-Y, Song E-J, Nam Y-D, Kim H (2024) Ginseng extracts improve circadian clock gene expression and reduce inflammation directly and indirectly through gut microbiota and PI3K signaling pathway. NPJ Biofilms Microbiomes 10:24. https://doi.org/10.1038/s41522-024-00498-5

Zhang Y, Li Y, Noya SB, Sehgal A (2024b) The Microbiome Interacts with the Circadian Clock and Dietary Composition to Regulate

Metabolite Cycling in the Gut. https://doi.org/10.7554/eLife.97130.1

Zhang M, Zhou C, Li X, Li H, Han Q, Chen Z, Tang W, Yin J (2025) Interactions between gut microbiota, host circadian rhythms, and metabolic diseases. Adv Nutr 16:100416. https://doi.org/10.1016/j.advnut.2025.100416

Zhao E, Tait C, Minacapelli CD, Catalano C, Rustgi VK (2022) Circadian rhythms, the gut microbiome, and metabolic disorders. Gastro Hep Adv 1:93–105. https://doi.org/10.1016/j.gastha.2021.10.008

Zimmermann P, Kurth S, Pugin B, Bokulich NA (2024) Microbial melatonin metabolism in the human intestine as a therapeutic target for dysbiosis and rhythm disorders. NPJ Biofilms Microbiomes 10:139. https://doi.org/10.1038/s41522-024-00605-6