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The Effects of Food on Circadian Rhythm: A Comprehensive Review

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ABSTRACT

Circadian rhythms regulate essential physiological functions such as metabolism, hormone secretion, and sleep–wake cycles. While light entrains the central clock in the suprachiasmatic nucleus (SCN), food serves as a powerful zeitgeber (an external environmental cue that synchronizes biological rhythms) for peripheral clocks, especially in metabolic tissues. Disruptions in meal timing, composition, or regularity can desynchronize these clocks and contribute to metabolic disorders. This review synthesizes current evidence on how dietary factors influence circadian regulation. We describe key nutrient-sensing pathways (AMPK, mTOR, SIRT1) and their role in clock gene modulation. The effects of macronutrients, micronutrients, and specific components—including fiber, phytochemicals, caffeine, and alcohol—on circadian physiology are examined in detail. We also explore the impact of meal timing strategies such as time-restricted feeding and discuss dietary considerations for shift workers and other at-risk populations. By integrating mechanistic insights with evidence-based dietary recommendations—such as optimal meal timing, macronutrient distribution, and nutrient-specific strategies, this review highlights the role of diet as a modifiable factor for circadian health. Aligning food intake with endogenous rhythms offers a promising strategy for improving metabolic outcomes and preventing circadian disruption in modern lifestyles.

1 | Introduction

Circadian rhythms refer to the endogenous, approximately 24-h cycles that govern the behavior, physiology, and metabolism of organisms, including humans (Dibner et al. 2010). These rhythms are orchestrated by an internal timekeeping mechanism known as the "circadian clock," which is present in nearly all cells of the body (Takahashi 2017). The term "circadian" is derived from the Latin words "circa" (around) and "diem" (day), emphasizing the daily nature of these rhythms (Halberg 1959). Circadian rhythms are essential for coordinating various physiological processes such as sleep-wake cycles, metabolism, hormone release, and immune function to adapt to daily environmental changes (Panda 2016). These rhythms are shaped by external zeitgebers (e.g., light) and internal factors (e.g., genetics), with food emerging as a key modulator of peripheral clocks.

Unlike light, which primarily regulates the central clock in the SCN, food plays a more direct role in modulating peripheral clocks through metabolic signals. This specificity in regulation makes food a controllable target for interventions aimed at correcting circadian rhythm disruptions. The potential to

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influence circadian health through dietary strategies further underscores the significance of understanding how food interacts with circadian biology.

The role of circadian rhythms in human health is well established, with disruptions linked to a wide range of adverse health outcomes, including sleep disorders, metabolic syndrome, and mental health issues. Disruptions in circadian rhythms have also been associated with conditions such as obesity, Type 2 diabetes, and cardiovascular diseases (Rutters et al. 2014). Furthermore, disturbances in circadian regulation can impair immune function and have been implicated in mental health disorders like major depressive disorder and bipolar disorder (McClung 2013). These findings underscore the importance of understanding and maintaining proper circadian rhythm regulation.

Given the significant impact of circadian rhythms on human health, maintaining proper synchronization of these rhythms is crucial. While light exposure and sleep patterns are the most well-known synchronizers, emerging evidence highlights the role of food in regulating circadian rhythms. Both meal timing and nutrient composition have been shown to influence the circadian system, with food acting as a potent zeitgeber for peripheral clocks in metabolic tissues such as the liver, adipose tissue, and muscle (Asher and Sassone-Corsi 2015; Damiola et al. 2000). The timing of food intake can reinforce the body's internal clock, helping synchronize metabolic processes with the central clock in the SCN, the master pacemaker of circadian rhythms (Panda 2016). Moreover, nutrient-sensing pathways such as mTOR, AMPK, and SIRT1 link nutrient availability to the regulation of circadian clock genes, affecting metabolic responses to feeding and fasting (Lamia et al. 2009; Um et al. 2007).

However, current research often focuses on single nutrients or mechanisms, leaving a gap in the understanding of the complex "food component - timing - peripheral clocks - health" network. Addressing this gap requires an integrated perspective that links mechanistic insights with dietary patterns and timing strategies, and this review aims to fill this gap by systematically integrating findings on how various food components influence circadian rhythms, particularly the peripheral clocks, and their implications for health. We will examine the influence of meal timing, macronutrient composition, and specific nutrients (carbohydrates, proteins, fats) on circadian rhythm regulation and metabolism. Additionally, we will address the implications of irregular eating patterns, such as those experienced by shift workers, and how strategies like time-restricted feeding (TRF) can help optimize circadian health. By providing an evidence-based understanding of the ways in which food interacts with the circadian system, this review aims to offer practical recommendations for improving health through dietary interventions that align with the body's natural rhythms.

2 | Physiological Basis of Circadian Rhythm and Its Regulation

2.1 | The Biological Clock and Its Components

The circadian clock is an endogenous timekeeping system that enables organisms to anticipate and adapt to the 24-h light–dark cycle. It regulates a broad range of physiological functions, including sleep–wake behavior, hormone secretion, immune responses, and metabolic homeostasis (Panda 2016; Takahashi 2017). This system consists of a central pacemaker and multiple peripheral oscillators that operate in a coordinated manner to maintain temporal stability across tissues (Dibner et al. 2010).

At the core of the circadian system lies the central clock, located in the SCN of the hypothalamus. Comprising approximately 20,000 neurons, the SCN receives direct photic input from intrinsically photosensitive retinal ganglion cells via the retinohypothalamic tract (RHT). This light signal entrains the SCN's oscillatory activity, allowing internal physiological rhythms to align with the external day–night cycle (Hattar et al. 2002; Welsh et al. 1995). The SCN subsequently communicates timing cues to peripheral clocks via both neural and humoral pathways—most notably through rhythmic cortisol secretion—ensuring systemic synchronization of behavioral and metabolic outputs (Kalsbeek et al. 2010; Schibler et al. 2003).

As illustrated in Figure 1a, this hierarchical structure places the SCN at the apex of the circadian system, receiving light cues and coordinating peripheral clocks located in metabolically active organs such as the liver, intestine, heart, and skeletal muscle. These peripheral oscillators exhibit tissue-specific rhythmicity but rely on SCN-driven outputs to maintain internal coherence. External behaviors such as feeding and sleep, which align with light and fasting cycles, further shape the phase of these oscillators.

At the cellular level, circadian rhythms are generated by interlocked transcriptional–translational feedback loops. The core loop involves CLOCK and BMAL1, two transcription factors that heterodimerize and bind to E-box elements in the promoters of *Period* (*PER1*, *PER2*, *PER3*) and *Cryptochrome* (*CRY1*, *CRY2*) genes, initiating their transcription (Gekakis et al. 1998). As PER and CRY proteins accumulate in the cytoplasm, they form inhibitory complexes that translocate into the nucleus and suppress CLOCK:BMAL1 activity, thus closing the feedback loop (Reppert and Weaver 2002). This cycle spans approximately 24 h and serves as the molecular basis for circadian rhythmicity.

As shown in Figure 1b, the precision and stability of this feedback mechanism are modulated by post-translational processes. Casein kinase 1 isoforms (CK1ε/δ) phosphorylate PER proteins, targeting them for proteasomal degradation. SCF-type E3 ubiquitin ligases, such as FBXL3 and β-TrCP, mediate the selective turnover of CRY and PER proteins, respectively, thereby adjusting the timing and amplitude of the oscillation (Eide et al. 2005; Zheng et al. 2016). These molecular mechanisms are conserved across central and peripheral clocks, providing a robust internal rhythm that integrates with external environmental cues.

2.2 | The Role of the SCN in Circadian Rhythm Regulation

As the central pacemaker of the mammalian circadian system, the SCN governs the synchronization of internal physiological rhythms with environmental cycles (Welsh et al. 1995). Through its influence on hormone secretion, metabolism, and

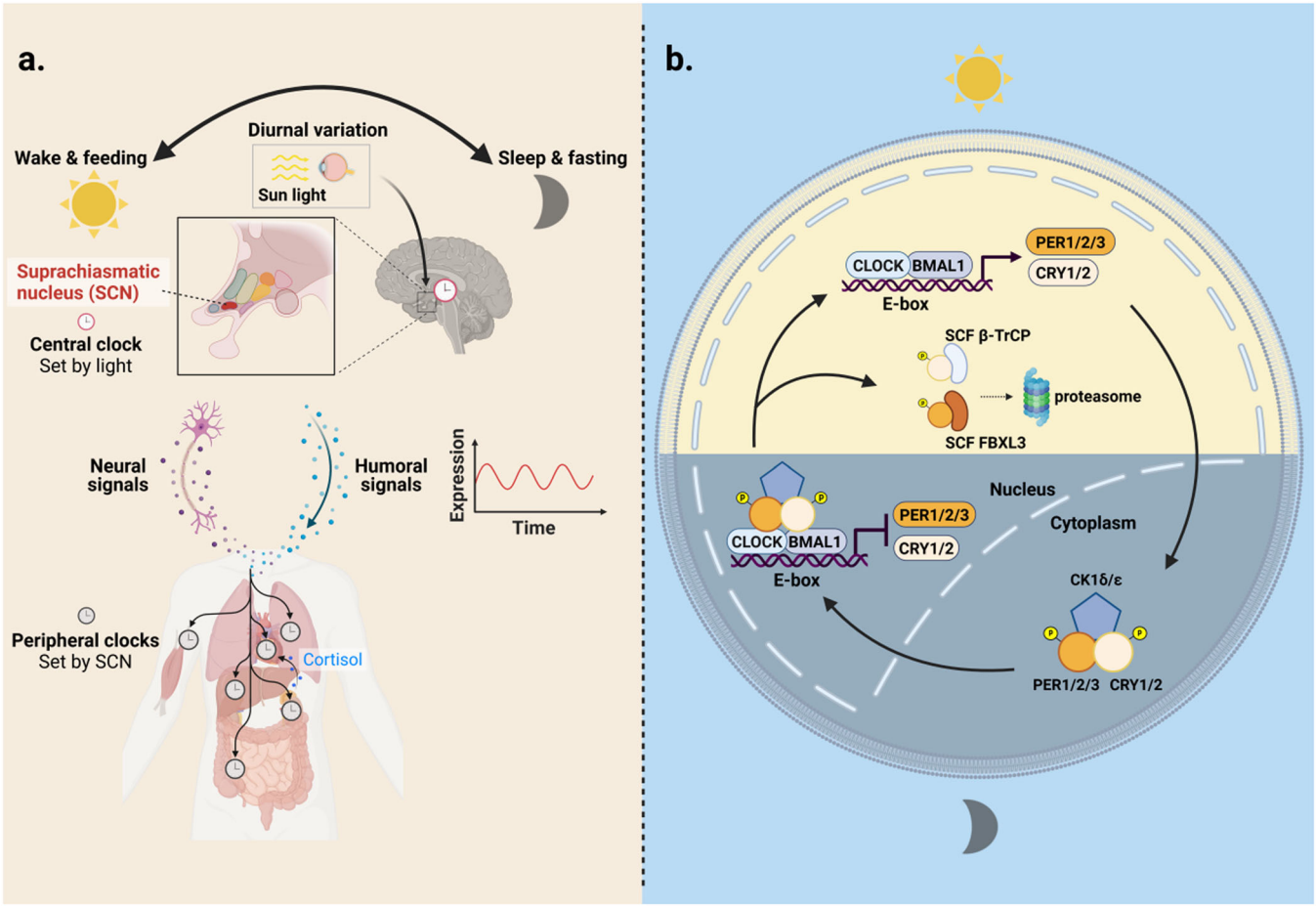

FIGURE 1 | Central and molecular mechanisms underlying circadian rhythm regulation. (a) Light signals are received by the retina and transmitted to the SCN, the master circadian clock, which synchronizes peripheral clocks in metabolic tissues via neural and humoral pathways (e.g., cortisol). (b) The molecular clock is governed by a transcriptional-translational feedback loop. CLOCK and BMAL1 heterodimers activate *PER* and *CRY* genes, whose translated proteins inhibit CLOCK/BMAL1 activity in an approximately 24-h cycle. Post-translational modifications (e.g., phosphorylation by CK1, degradation via SCF complexes) fine-tune the timing and robustness of the oscillation.

behavior, the SCN plays a pivotal role in maintaining temporal homeostasis (Dibner et al. 2010).

Light serves as the primary zeitgeber for SCN entrainment. Specialized retinal ganglion cells transmit light information to the SCN via the RHT, where glutamate and the neuropeptide PACAP (pituitary adenylate cyclase-activating polypeptide) trigger intracellular signaling cascades that reset its oscillations (Hattar et al. 2002). Unlike food cues—which primarily entrain peripheral clocks through metabolic pathways—light acts directly on the central pacemaker, underscoring a functional distinction between external inputs (Asher and Sassone-Corsi 2015).

Within the SCN, circadian rhythms are sustained by synchronized activity among thousands of neurons expressing oscillatory genes such as *PER1*, *PER2*, *CRY1*, and *BMAL1* (Takahashi 2017). These oscillations are reinforced by neuropeptide-mediated coupling mechanisms, including the release of vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP), which maintain robust and coherent rhythmic output (Aton and Herzog 2005; Kalsbeek et al. 2010; Maywood et al. 2011). This tight neuronal coupling enables the SCN to act as a unified temporal signal generator.

The SCN communicates temporal cues to peripheral tissues through both hormonal and neural pathways. It regulates the rhythmic secretion of melatonin from the pineal gland and orchestrates daily patterns of cortisol, insulin, and other metabolic hormones (Kalsbeek et al. 2010; Moore 1996). Importantly, SCN-regulated signals are not unidirectional. For instance, the morning cortisol peak facilitates hepatic glucose mobilization, but this effect is modulated by breakfast timing—highlighting reciprocal interactions between central outputs and food-derived metabolic responses (Farshchi et al. 2005).

While the SCN maintains top-down control over peripheral oscillators, feeding at abnormal circadian times can modulate metabolic rhythms independently of SCN signals—particularly in tissues like the liver and adipose tissue (Damiola et al. 2000). This adaptive flexibility supports nutrient-driven prioritization (Asher and Sassone-Corsi 2015).

2.3 | External and Internal Factors Affecting Circadian Rhythm

Circadian rhythms are shaped by a complex interplay between environmental cues and internal physiological states. Among the

external influences, light is the most potent zeitgeber for the central clock located in the SCN. Retinal input synchronizes SCN activity with the light–dark cycle, primarily influencing neuroendocrine and behavioral rhythms (Hattar et al. 2002; Khalsa et al. 2003). However, light's effect is largely confined to the central oscillator, whereas food intake serves as a powerful entraining signal for peripheral clocks, particularly those in metabolic tissues (Asher and Sassone-Corsi 2015). This distinction highlights the unique regulatory domain of feeding behavior.

Other environmental factors such as ambient temperature have only modest effects on circadian rhythms in mammals. Although temperature is a strong entrainment cue in ectotherms, its role in humans is limited and far less influential than that of food (Manoogian and Panda 2017). Social interactions—often considered secondary zeitgebers—exert circadian influence primarily through structured behaviors like shared meal times, work shifts, and social activity patterns. In this context, meal timing serves as both a social and physiological cue, reinforcing feeding's critical role in peripheral clock synchronization (Mistlberger and Skene 2004).

Internal factors also modulate circadian regulation and interact with food-related rhythms. Genetic polymorphisms in core clock genes, such as *PER2* and *CRY1*, not only influence individual chronotype but also affect responses to dietary interventions. For example, carriers of certain *PER2* variants exhibit attenuated metabolic adaptation to TRF, suggesting that gene-diet interactions modulate circadian alignment (Archer et al. 2003; Patke et al. 2017).

Hormonal rhythms, often governed by the SCN, are reciprocally shaped by nutrient intake. The cortisol peak in the early morning facilitates gluconeogenesis, but this response is amplified by breakfast consumption. Conversely, melatonin secretion can be suppressed by late-evening carbohydrate intake, illustrating bidirectional crosstalk between endocrine oscillations and feeding behavior (Gooley et al. 2011; Kalsbeek et al. 2010).

Age is another intrinsic factor that alters circadian rhythmicity. With advancing age, rhythm amplitude declines and sleep-wake patterns become fragmented. However, dietary strategies—such as maintaining regular meal schedules or increasing fiber intake—have been shown to partially restore peripheral oscillation robustness in older adults (Hofman and Swaab 2006; St-Onge et al. 2017). These findings underscore the role of nutrition as a modifiable factor capable of mitigating age-related circadian deterioration.

While external cues like light and internal traits like genetics establish baseline rhythms, food intake functions as a dynamic bridge between these systems. It not only entrains peripheral clocks but also mediates the interactions between central and peripheral oscillators, even under conditions of physiological constraint or environmental misalignment.

2.4 | The Impact of Food on the Biological Clock

While the SCN serves as the central circadian pacemaker, maintaining organism-wide rhythmicity through light entrainment, peripheral clocks—particularly those in metabolic tissues—are highly sensitive to feeding-related cues. This division of labor allows organisms to prioritize metabolic responses to nutrient availability over photic inputs under certain conditions (Asher and Sassone-Corsi 2015; Dibner et al. 2010). Unlike light, which primarily influences the SCN via the RHT, food acts as a dominant zeitgeber for peripheral oscillators and can even uncouple them from central control during mistimed feeding or fasting cycles (Damiola et al. 2000; Manoogian and Panda 2017).

Figure 2 illustrates this dual-entrainment framework. Light information is received by melanopsin-expressing retinal ganglion cells and transmitted via the RHT to the SCN, where glutamate and PACAP serve as primary neurotransmitters. The SCN, in turn, synchronizes peripheral clocks—such as those in the liver, adipose tissue, muscle, and gastrointestinal tract—through neural and hormonal outputs (e.g., cortisol rhythms). In contrast, food cues directly entrain peripheral clocks through nutrient-sensitive signaling pathways that bypass the SCN, providing tissue-specific temporal regulation.

At the molecular level, nutritional cues modulate circadian timing via key nutrient-sensing pathways. AMPK, activated under low energy conditions, promotes CRY degradation and advances clock phase (Lamia et al. 2009). In contrast, mTOR responds to nutrient abundance and modulates PER2 stability through phosphorylation, influencing the periodicity of the circadian loop (Um et al. 2007). SIRT1, activated by NAD^+ during fasting, links redox state and feeding–fasting cycles to transcriptional regulation of core clock genes via BMAL1 and PER2 deacetylation (Nakahata et al. 2008).

These molecular pathways are differentially expressed across tissues, rendering some peripheral clocks more responsive to feeding cues. For example, the liver exhibits robust shifts in *PER2* expression in response to glucose or protein ingestion, even in the absence of SCN signaling (Damiola et al. 2000). Adipose tissue and skeletal muscle clocks are likewise sensitive to fatty acids and branched-chain amino acids, while intestinal clocks respond to microbiota-derived metabolites such as short-chain fatty acids (SCFAs), which are produced rhythmically through fiber fermentation.

Moreover, specific macronutrients exert distinct circadian effects. Carbohydrates modulate insulin and glucose rhythms; proteins influence amino acid signaling and melatonin synthesis via tryptophan metabolism; and fats—especially saturated fats—dampen clock gene amplitude and induce peripheral desynchronization. Dietary fiber enhances SCFA production and microbial rhythmicity, thereby reinforcing gut–brain clock communication and synchronizing gastrointestinal clocks with feeding behavior (Thaiss et al. 2014).

3 | The Nutrient Timing Hypothesis in the Context of Circadian Biology

3.1 | Definition and Basis of the Nutrient Timing Hypothesis

The nutrient timing hypothesis posits that the strategic ingestion of specific nutrients—such as carbohydrates, proteins, and

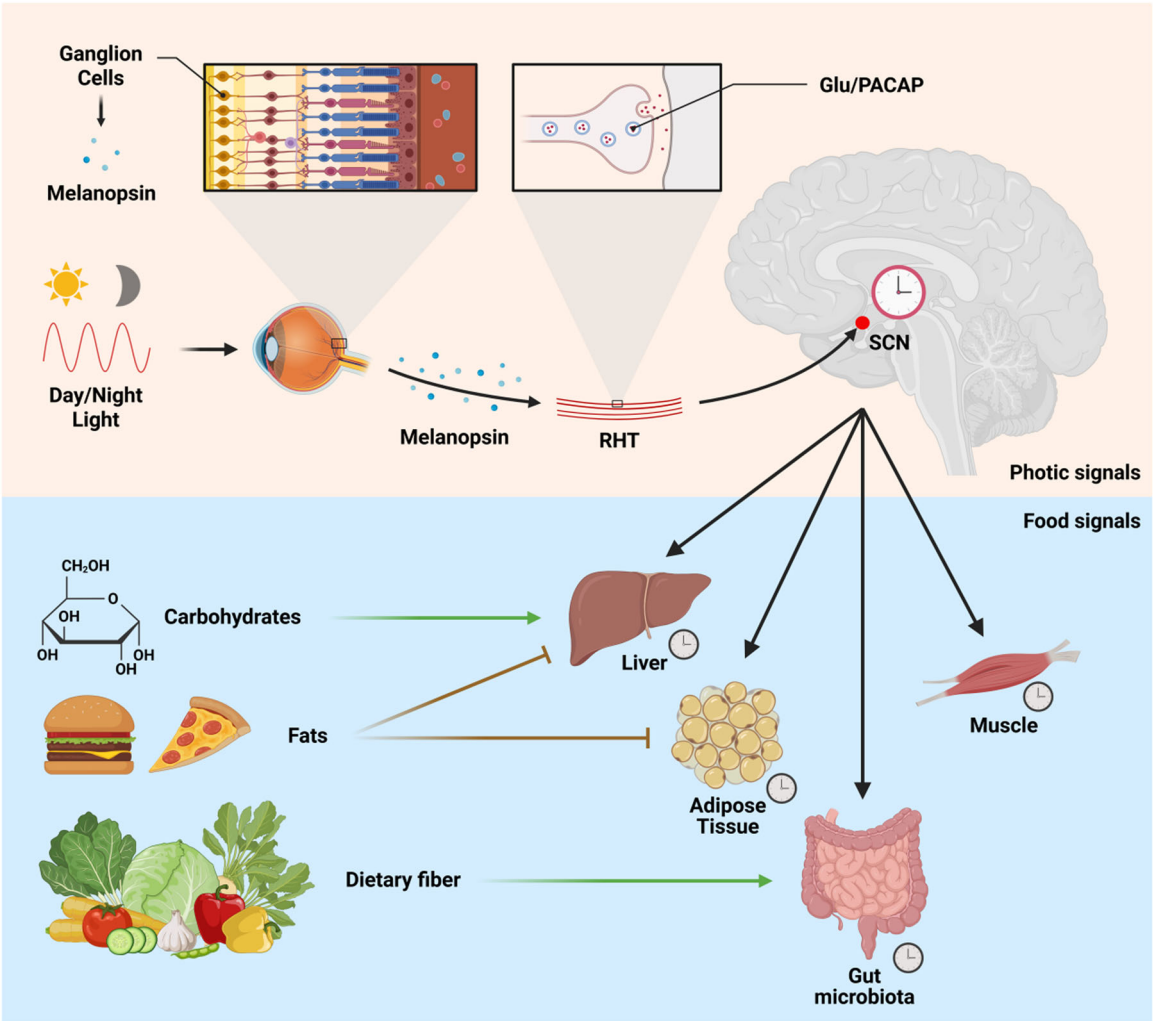

FIGURE 2 | Comparison of light signal transduction pathway and food signal regulation pathway. After receiving the light signal, retinal ganglion cells transmit the signal to the retinohypothalamic tract through melanopsin. With glutamate/pituitary adenylate cyclase-activating polypeptide (PACAP) as the main transmitter, the signal is transmitted to the SCN, which regulates the circadian rhythm of the liver, adipose tissue, intestine, muscle, etc. Food as a zeitgeber: In the food signal regulation, carbohydrate represented by glucose has a rhythmic regulation effect on the liver, food rich in dietary fiber plays a regulatory role on the intestinal flora, and dietary fat has a negative impact on the rhythmic regulation of the liver and adipose tissue.

amino acids—at times aligned not only with physiological demands (e.g., exercise) but also with endogenous circadian rhythms can enhance metabolic efficiency, muscle recovery, and overall health outcomes (Aragon and Schoenfeld 2013). Originally rooted in sports nutrition, this hypothesis has since expanded to encompass chronobiological perspectives, recognizing that nutrient utilization and hormonal responses fluctuate across the 24-h cycle (Arent et al. 2020).

Pre-exercise carbohydrate intake is widely used to optimize glycogen availability and improve endurance capacity. Recent findings suggest that this effect is amplified when aligned with the circadian peak in glucose uptake capacity, as *GLUT4* expression in skeletal muscle is highest in the early active phase, typically in the morning for diurnal humans (Barnea et al. 2009; Edinburgh et al. 2020). Protein or essential amino acid ingestion before resistance training may also benefit muscle protein synthesis, particularly when administered during periods of elevated anabolic signaling potential.

During prolonged physical activity, carbohydrate-electrolyte solutions help maintain blood glucose levels and hydration, while amino acids may attenuate muscle protein breakdown. These effects, however, are influenced by circadian variations in substrate oxidation and metabolic enzyme activity, which can modulate the efficiency of nutrient utilization (Cermak and van Loon 2013; Shimomura et al. 2004).

Post-exercise nutrient timing has traditionally emphasized the "anabolic window"—often described as the approximately 30–60 min immediately following exercise—during which muscle sensitivity to amino acids and carbohydrates is thought to be maximized. However, more recent studies suggest that this window may extend for several hours, with its duration and magnitude influenced by factors such as exercise type, training status, and circadian phase. For example, insulin sensitivity tends to peak in the afternoon, enhancing postprandial amino acid uptake and glycogen synthesis during that time (Rutters et al. 2014). Similarly, mTOR, a key nutrient-sensing kinase that

regulates protein synthesis, exhibits circadian oscillations, with activity peaking during the active phase and declining during the rest phase (Um et al. 2007).

Although some researchers argue that total daily nutrient intake has a more pronounced effect than timing alone (Aragon and Schoenfeld 2013), growing evidence suggests that circadian misalignment—such as high protein intake during the biological night—may attenuate anabolic responses, even when total intake is adequate (Kent et al. 2022). These findings underscore the need to integrate nutrient timing strategies with circadian biology to optimize metabolic adaptation.

3.2 | Evidence Supporting the Nutrient Timing Hypothesis

While the nutrient timing hypothesis originated in the context of exercise performance, an expanding body of empirical research supports its broader physiological relevance. Studies increasingly show that aligning nutrient intake with circadian variations in metabolism and hormonal responsiveness can influence energy balance, glucose regulation, and anabolic efficiency.

One line of evidence focuses on the time-of-day effects on glucose homeostasis. Identical meals consumed in the morning versus the evening produce significantly different glycemic and insulinemic responses, likely reflecting circadian fluctuations in β-cell activity and insulin sensitivity (Morris et al. 2015). Early time-restricted feeding (eTRF), for example, has been shown to improve glycemic control, reduce postprandial glucose excursions, and enhance lipid metabolism, suggesting that morning-oriented intake is metabolically favorable (Sutton et al. 2018). Conversely, late-night eating or skipping breakfast impairs glucose tolerance, blunts thermogenesis, and increases cardiometabolic risk—effects attributed to circadian misalignment between nutrient availability and the rhythmic expression of glucose transporters and metabolic enzymes (Jakubowicz et al. 2013; LeCheminant et al. 2013).

Additional support for the nutrient timing hypothesis comes from the circadian regulation of hormonal and gastrointestinal responses. Incretins such as GLP-1, which potentiate insulin secretion, display stronger postprandial release in the morning, aligning with enhanced metabolic readiness earlier in the day (Huber et al. 2024). Cortisol, a hormone with a well-defined circadian rhythm, peaks in the early morning and works synergistically with breakfast intake to promote glucose mobilization and appetite regulation (Farshchi et al. 2005). These hormonal rhythms not only shape metabolic outputs but also interact with feeding patterns in a time-dependent manner.

Furthermore, nutrient timing affects exercise recovery and muscle anabolism. Protein intake following physical activity is more effective during the active phase, when mTOR signaling and insulin responsiveness are naturally elevated, thus optimizing muscle protein synthesis (Rutters et al. 2014; Um et al. 2007). The commonly cited "anabolic window" may therefore reflect a circadian amplification of nutrient-driven anabolic pathways, rather than simply an acute post-exercise phenomenon.

3.3 | Limitations and Criticisms of the Nutrient Timing Hypothesis

While the nutrient timing hypothesis holds intuitive appeal, its implementation in both research and practice remains fraught with challenges—particularly when viewed through the lens of circadian biology. Several key controversies have emerged regarding its mechanisms, empirical evidence, and clinical translation, many of which can be better understood by integrating insights from circadian physiology.

One persistent debate centers on the primacy of total nutrient intake versus the timing of intake. While some argue that total daily consumption of macronutrients is the dominant determinant of health outcomes (Aragon and Schoenfeld 2013), mounting evidence suggests that this relationship is modulated by circadian rhythms. For example, protein consumed during the biological night may have diminished anabolic effects due to suppressed mTOR activity and reduced amino acid transporter expression (Edinburgh et al. 2020; Um et al. 2007). This implies that nutrient timing is not merely a secondary factor, but a physiological modulator of nutrient efficacy across the 24-h cycle.

Another critical issue lies in methodological oversights that undermine the interpretability of nutrient timing studies. Many trials fail to control for participants' chronotype (e.g., morningness vs. eveningness), habitual sleep-wake timing, or the circadian phase at which blood samples are collected. For instance, studies aggregating data from both morning and evening training sessions may obscure genuine time-of-day effects on insulin sensitivity, which peaks in the late afternoon (Rutters et al. 2014). Without accounting for these variables, inconsistent findings across studies may reflect underlying circadian misalignment rather than the ineffectiveness of nutrient timing itself.

A third controversy concerns the traditional concept of the "anabolic window," which suggests that nutrients must be consumed within 1–2 h post-exercise to optimize recovery. This model, however, may oversimplify a dynamic process shaped by the internal clock. Circadian oscillations in clock-controlled genes such as *PER2* and nutrient transporters like LAT1 suggest that nutrient absorption and utilization capacities vary across the day (Edinburgh et al. 2020). Thus, the metabolic "window" may shift or widen depending on the circadian phase, questioning the universality of fixed post-exercise guidelines.

Finally, the translational application of nutrient timing strategies poses significant challenges in real-world contexts. Individuals with circadian disruption—such as shift workers or those experiencing chronic jet lag—exhibit altered metabolic responses to food, diminished insulin sensitivity, and dysregulated clock gene expression (Archer and Oster 2015; Oosterman et al. 2020). These factors highlight the need for personalized chrono-nutritional interventions that consider both lifestyle patterns and biological timing.

Emerging technological advances—such as continuous glucose monitoring, wearable circadian phase trackers, high-throughput multi-omics profiling, and machine learning–based chronotype assessment—together with refined experimental designs (e.g.,

daily time-of-day control in phase-synchronized individuals) may address some of these issues.

4 | Impact of Meal Timing on Circadian Rhythm

4.1 | The Role of Breakfast in Synchronizing Circadian Rhythm

Breakfast plays a critical role in circadian alignment by serving as a metabolic cue that entrains peripheral clocks and coordinates hormonal, behavioral, and metabolic rhythms. As a potent zeitgeber, breakfast primarily influences peripheral tissues such as the liver, pancreas, and adipose tissue, operating in parallel with light-driven entrainment of the central clock in the SCN. Through nutrient-sensing pathways like AMPK and mTOR, breakfast initiates phase resetting of clock gene expression (e.g., *BMAL1*, *PER2*) in response to feeding cues (Dibner et al. 2010; Potter et al. 2016). This synchronization is reinforced by hormonal regulation: morning cortisol peaks—modulated by SCN signals—are enhanced by breakfast intake, which promotes *REV-ERBα* expression in hepatic tissue. Simultaneously, insulin secretion triggered by postprandial glucose activates mTOR signaling and phosphorylates PER proteins, further aligning peripheral oscillators with the active phase (Lamia et al. 2009). These endocrine effects contribute to enhanced diet-induced thermogenesis in the morning, mediated by clock-controlled genes like *UCP1* in adipose tissue (Basolo et al. 2021). In contrast, breakfast skipping blunts thermogenic responses and disrupts appetite-regulating hormones such as leptin and ghrelin, predisposing individuals to increased hunger and impaired glycemic control later in the day (Farshchi et al. 2005). Furthermore, consistent morning eating reinforces temporal alignment between the SCN's sleep-wake output and downstream metabolic processes. Jakubowicz et al. (2013) reported that high-energy breakfast intake advanced melatonin onset and improved sleep onset timing, likely mediated through pineal *PER1* expression (Jakubowicz et al. 2013). Notably, the composition of breakfast also shapes its chronobiological effects: meals high in protein and fiber support stable insulin and cortisol rhythms, whereas sugar-dense breakfasts may induce glycemic spikes and circadian misalignment (Afaghi et al. 2007; Phillips et al. 1975).

4.2 | Effects of Late-Night Eating on Circadian Rhythm

Late-night eating has emerged as a potent disruptor of circadian organization, primarily by acting as a mistimed zeitgeber that induces phase misalignment between central and peripheral clocks. While the SCN remains synchronized to the light–dark cycle, food intake during the biological night drives peripheral clocks—particularly in the liver and adipose tissue—into an alternate phase, resulting in desynchronization of clock-controlled metabolic processes (Damiola et al. 2000; Petersen et al. 2022).

This phase misalignment is underpinned by shifts in the expression of core clock genes. Nocturnal feeding induces an aberrant upregulation of *CRY1* and suppression of *BMAL1* in hepatic tissue, effectively inverting their normal oscillatory patterns (Kohsaka et al. 2007). Such inversion disrupts the rhythmicity of key metabolic enzymes like glucokinase, impairing glucose homeostasis. In extreme cases, the phase difference between SCN-driven central rhythms and food-driven peripheral oscillators can exceed 4 h—a threshold associated with metabolic dysfunction (Petersen et al. 2022).

Late-night meals also alter endocrine rhythms, compounding circadian misalignment. Carbohydrate-rich evening intake suppresses melatonin secretion by 30%–50%, delaying sleep onset and attenuating melatonin-mediated activation of hepatic *REV-ERBα*, a nuclear receptor critical for lipid metabolism rhythm (Gooley et al. 2011; Teeple et al. 2023). This reduction in *REV-ERBα* activity leads to desynchronization of fatty acid oxidation from the central clock. Concurrently, late feeding activates the hypothalamic–pituitary–adrenal (HPA) axis, elevating evening cortisol levels that should be declining. This abnormal cortisol peak upregulates *PER1* in adipose tissue and suppresses leptin's nocturnal surge, weakening satiety signaling and promoting overeating (Gonnissen et al. 2012). Additionally, ghrelin secretion, which normally peaks before dawn, is advanced, increasing nocturnal hunger and reinforcing maladaptive intake cycles.

The metabolic consequences of these disruptions are evident in impaired glucose and lipid regulation. Postprandial hyperglycemia is exacerbated at night due to reduced hepatic glucose clearance—a result of *BMAL1*-dependent *GLUT2* expression being desynchronized from feeding cues (Sato et al. 2011). Similarly, lipid oxidation is suppressed as the oscillation of hormone-sensitive lipase (HSL)—a key enzyme in lipid breakdown regulated by *PER2*—is blunted. When *PER2* rhythms are misaligned, HSL remains inactive during the night, facilitating triglyceride accumulation and increasing adiposity risk (Arredondo-Amador et al. 2020; Basolo et al. 2021).

In contrast to breakfast, which reinforces synchronization between the SCN and peripheral metabolic tissues, late-night eating creates a temporal conflict by delivering feeding signals during the biological rest phase. This misalignment compromises hormonal, molecular, and metabolic rhythmicity, laying the groundwork for long-term metabolic disorders such as insulin resistance, dyslipidemia, and obesity.

4.3 | Shift Work, Irregular Meal Times, and Circadian Disruption

Beyond individual meal timing choices, broader societal factors such as shift work and erratic lifestyles also pose significant challenges to circadian health. Modern lifestyles increasingly involve shift work and irregular eating schedules—two behaviors that profoundly disrupt circadian organization. Night-shift workers are frequently exposed to artificial light during the biological night, suppressing melatonin secretion and delaying the phase of the central clock located in the SCN (Kecklund and Axelsson 2016). This light-induced phase shift alters the expression of core clock genes, such as *PER2* and *CRY1*, and decouples the SCN from peripheral oscillators. The resulting misalignment—often termed “social jetlag”—has been linked to

sleep disturbances, cognitive impairment, and chronic fatigue (Wright et al. 2013).

Concurrently, shift work is commonly associated with mistimed and irregular eating patterns. Unlike the SCN, which is entrained by light, peripheral clocks in the liver, pancreas, adipose tissue, and gastrointestinal tract are strongly responsive to feeding cues (Potter et al. 2016). Consuming meals during the biological night induces phase shifts in peripheral clocks independent of SCN control, leading to disrupted rhythmic expression of genes such as *BMAL1* and *PER2*. This desynchronization impairs glucose tolerance, alters lipid metabolism, and contributes to hormonal imbalances. Mechanistically, late-night eating activates nutrient-sensing pathways like AMPK and mTOR at circadian-inappropriate times, dampening metabolic efficiency and increasing the risk of insulin resistance (McHill et al. 2014).

These circadian disruptions have been implicated in a wide range of adverse health outcomes. Shift workers exhibit a significantly elevated risk of obesity and Type 2 diabetes, attributed in part to reduced insulin sensitivity and impaired hepatic glucose regulation (Al-Naimi et al. 2004). Cardiovascular health is also compromised, as cortisol rhythms become blunted and sympathetic nervous activity is elevated during the biological night, increasing the likelihood of hypertension and coronary artery disease. Moreover, gastrointestinal disturbances—including dyspepsia and altered bowel patterns—arise from misaligned gut motility and microbial oscillations. Neurologically, disrupted melatonin secretion and chronic sleep fragmentation impair cognitive performance and emotional regulation over time.

To mitigate these risks, targeted interventions have been proposed. Aligning food intake with the active phase—even during night shifts—can help preserve peripheral clock integrity. Controlled exposure to bright light during waking hours and avoidance of light during the biological night may aid in SCN re-entrainment. Personalized scheduling strategies that account for individual chronotype and circadian responsiveness are also gaining attention as tools to reduce the burden of shift-related circadian misalignment.

4.4 | TRF and Its Effects on Circadian Rhythm

TRF is a dietary strategy that confines caloric intake to a defined daily window, typically spanning 6–12 h, without altering total caloric intake. Unlike calorie restriction or macronutrient manipulation, TRF aligns eating patterns with endogenous circadian rhythms, thereby functioning as a behavioral zeitgeber that reinforces the synchrony between feeding behavior and the body's internal clocks (Chaix et al. 2019).

Mechanistically, TRF exerts its effects by restoring the temporal structure of nutrient signaling in peripheral tissues. During fasting periods, elevated NAD^+ levels activate the nutrient-sensing deacetylase SIRT1, which promotes the rhythmic deacetylation of PER2 and BMAL1 proteins—enhancing the precision and amplitude of the molecular clock (Jenwitheesuk et al. 2014). Concurrently, energy restriction activates AMPK, leading to CRY1 destabilization and facilitating circadian phase resetting in metabolic organs such as the liver and adipose tissue (Lamia et al. 2009). These effects collectively reestablish robust oscillations in clock gene expression that are often dampened by mistimed or continuous feeding.

Empirical studies have demonstrated that TRF improves metabolic parameters in both animal models and humans. In mice, restricting feeding to the active phase rescues high-fat diet (HFD)-induced disruptions in hepatic *BMAL1* and *PER2* expression, restores the rhythmicity of glucose transporter GLUT2, and reverses hepatic steatosis (Hatori et al. 2012). Similarly, in overweight humans, early TRF (e.g., 8 a.m. to 2 p.m.) enhances insulin sensitivity, lowers blood pressure, and increases fat oxidation compared to late eating schedules, highlighting the importance of aligning food intake with the circadian rhythm of insulin responsiveness (Basolo et al. 2021; Sutton et al. 2018). These benefits are thought to arise from improved coherence between the SCN-driven central clock and nutrient-responsive peripheral clocks.

Importantly, the timing of the feeding window critically influences its circadian efficacy. Morning TRF aligns more closely with the body's natural rhythms—particularly cortisol's early-day peak and the diurnal rise in insulin sensitivity—thereby producing stronger metabolic improvements than evening or mid-day TRF schedules (Petersen et al. 2022). This effect is particularly relevant for shift workers or individuals experiencing circadian misalignment, in whom TRF has been shown to partially restore rhythmic gene expression and attenuate metabolic dysfunction (Hatori et al. 2012).

Beyond metabolism, TRF may also support sleep and circadian behavioral rhythms. By eliminating late-night meals that suppress melatonin and elevate evening cortisol (as described in Section 4.2), TRF contributes to more stable hormonal oscillations and improved sleep quality. Recent findings also suggest that TRF reestablishes rhythmicity in the gut microbiota and associated SCFA production—factors increasingly recognized as modulators of SCN function via the gut-brain axis (Thaiss et al. 2014).

5 | The Role of Macronutrients in Circadian Rhythm Regulation

5.1 | Carbohydrates and Circadian Rhythm

Carbohydrates function as potent zeitgebers that influence the molecular and physiological components of circadian regulation, particularly in peripheral metabolic tissues. Their effects depend not only on the quantity and quality of carbohydrates consumed but also on the timing relative to endogenous circadian phase.

High-glycemic index (GI) carbohydrates lead to rapid postprandial glucose and insulin surges. Mechanistically, insulin activates the PI3K–Akt pathway, which modulates circadian gene expression through the phosphorylation and accelerated degradation of PER2, a key component of the negative feedback loop. This disrupts CLOCK–BMAL1 transcriptional activity and

alters the rhythmic expression of core clock genes such as *BMAL1* and *PER1* (Kohsaka et al. 2007; Um et al. 2007). In contrast, low-GI carbohydrates induce more gradual glycemic responses, minimizing insulin spikes and preserving circadian phase stability. Barnea et al. (2009) demonstrated that low-GI diets maintain robust hepatic expression of *CLOCK* and *CRY1*, supporting coherent temporal oscillations in metabolic tissues (Barnea et al. 2009).

In addition to modulating gene expression via insulin signaling, carbohydrate intake interacts with melatonin synthesis through tryptophan metabolism. Elevated insulin levels following carbohydrate-rich meals promote the uptake of large neutral amino acids (LNAAs) by skeletal muscle, thereby increasing the plasma tryptophan/LNAA ratio. This facilitates tryptophan transport across the blood–brain barrier, enhancing its conversion to serotonin and subsequently to melatonin in the pineal gland (Fernstrom 2013). While this may support evening melatonin production under appropriate conditions, excessive high-GI carbohydrate intake—especially at night—can suppress endogenous melatonin secretion through feedback inhibition and disrupt sleep architecture (Afaghi et al. 2007; Gooley et al. 2011).

Figure 3 summarizes these divergent physiological effects. High-GI carbohydrates elicit sharp glycemic and hormonal fluctuations that influence both peripheral clock gene expression and central melatonin synthesis, contributing to circadian phase delays. In contrast, low-GI carbohydrate intake supports stable blood glucose rhythms, maintains consistent *BMAL1* and *PER1* expression patterns, and preserves circadian phase integrity.

Furthermore, the timing of carbohydrate intake plays a critical role. Morning consumption of complex, low-GI carbohydrates aligns with circadian peaks in insulin sensitivity and thermogenesis, promoting metabolic efficiency and reinforcing central–peripheral clock synchrony. Conversely, evening intake of high-GI carbohydrates disrupts melatonin rhythms, suppresses *REV-ERBα* expression, and misaligns peripheral metabolic clocks with SCN-driven signals.

5.2 | Proteins and Circadian Rhythm

Dietary proteins, and more specifically individual amino acids, have been shown to modulate circadian rhythms through both central and peripheral mechanisms. Among these, tryptophan and branched-chain amino acids (BCAAs) are the most extensively studied. Tryptophan serves as the biochemical precursor to serotonin and melatonin, two critical modulators of circadian signaling. Increased availability of tryptophan enhances its transport across the blood–brain barrier, particularly when the plasma tryptophan/LNAA ratio is elevated, as discussed in Section 5.1. Once in the brain, tryptophan is converted into serotonin and subsequently into melatonin within the pineal gland, thereby influencing the amplitude and phase of the central circadian oscillator (Bubenik 2001; Fernstrom 2013).

In addition to its role in melatonin synthesis, protein intake also impacts peripheral circadian rhythms via nutrient-sensing pathways. BCAAs—including leucine, isoleucine, and valine—activate the mechanistic target of rapamycin complex 1 (mTORC1), a central hub in nutrient signaling. Activation of mTORC1 leads to phosphorylation of clock proteins such as PER2, promoting their ubiquitination and proteasomal degradation, which in turn modulates CLOCK:BMAL1 transcriptional activity and alters the period and amplitude of peripheral clocks (Cao 2018; Crosby and Partch 2020; Sahar and Sassone-Corsi 2009). These effects are particularly prominent in tissues with high metabolic turnover, such as the liver and skeletal muscle.

Dietary fats exhibit heterogeneous effects on circadian regulation depending on fatty acid composition. Saturated fatty acids (SFAs), especially palmitic acid, have been shown to destabilize PER2 and impair rhythmic gene expression in liver and adipose tissue, leading to dampened oscillations and phase shifts (Checa-Ros and D'Marco 2022; Shi et al. 2019). In contrast, omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert protective effects on circadian rhythms. These PUFAs serve as ligands for nuclear receptors, including REV-ERBα and PPARs, which regulate the transcription of core clock components and metabolic genes in a circadian manner (Checa-Ros and D'Marco 2022; Liu et al. 2021; Yao et al. 2024). The activation of REV-ERBα enhances the robustness of circadian oscillations in peripheral tissues and improves clock–metabolism alignment.

Figure 4 summarizes these nutrient-specific molecular pathways. Tryptophan contributes to central clock regulation via melatonin synthesis, while BCAAs influence peripheral oscillators through mTORC1–PER2 signaling. On the lipid side, SFAs impair PER2 stability and dampen rhythmicity, whereas omega-3 PUFAs activate nuclear receptors that enhance peripheral clock gene expression. These macronutrients thus exert bidirectional effects on circadian regulation, impacting both central and peripheral components of the clock system.

Overall, proteins and fats serve as bioactive modulators of the circadian system through their influence on gene expression, post-translational regulation, and hormonal outputs. Strategic modulation of amino acid and fatty acid intake—both in quantity and timing—may offer novel avenues for improving circadian alignment and metabolic resilience.

5.3 | Fats and Circadian Rhythm

In addition to proteins, which modulate circadian rhythms primarily through amino acid–driven pathways and hormonal regulation, dietary fats also exert profound and distinct influences on circadian physiology. Dietary fats play a multifaceted role in modulating circadian rhythms, acting through both nutrient-sensing pathways and hormone-regulated feedback mechanisms. The impact of fats on circadian physiology depends on their quantity, composition, and timing of intake, with distinct effects on central and peripheral clocks. HFDs, especially those rich in SFAs, have been shown to dampen the amplitude and phase coherence of core clock genes such as *BMAL1* and *PER2* in peripheral tissues like the liver and adipose tissue (Hatori et al. 2012; Kohsaka et al. 2007).

As shown in Figure 4, SFAs promote PER2 destabilization and circadian disruption, while omega-3 PUFAs enhance REV-ERBα activity, reinforcing rhythmic gene expression in peripheral

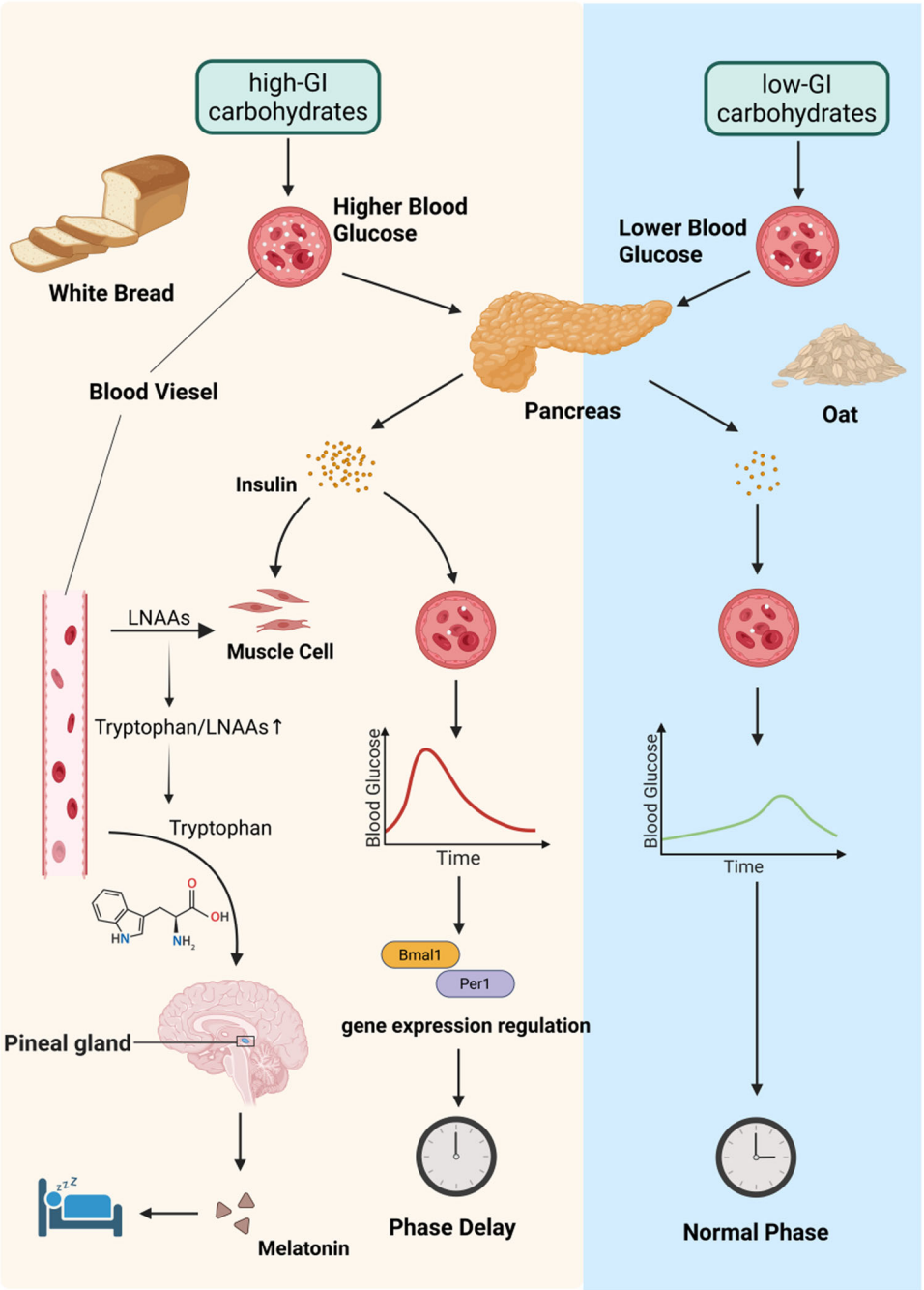

FIGURE 3 | Differences in the regulation of circadian rhythms by high-GI and low-GI carbohydrates in the diet. High-GI carbohydrates induce a rapid increase in blood glucose after consumption, prompting the pancreas to secrete high levels of insulin. This leads to a sharp drop in blood glucose while promoting the uptake of circulating LNAAs by muscle cells. The drastic fluctuations in blood glucose cause delayed expression of *BMAL1* and *PER1* genes, resulting in phase delay. An elevated tryptophan/LNAAs ratio in the blood enhances tryptophan uptake by the brain, thereby increasing melatonin synthesis. In contrast, low-GI carbohydrates do not cause drastic fluctuations in blood glucose after ingestion, which contributes to the stability of circadian clock phase.

tissues. Mechanistically, HFDs impair the rhythmic activation of nuclear receptors such as PPARα and REV-ERBα, which normally synchronize lipid oxidation and clock gene expression. This disruption desynchronizes metabolic outputs from the master clock, promoting a state of circadian misalignment. Inflammatory pathways further contribute: saturated fats activate NF-κB signaling and increase pro-inflammatory cytokines such as IL-6, which interfere with both hypothalamic clock output and peripheral gene oscillation.

Fatty acid composition also influences sleep–wake regulation. Saturated fats have been linked to reduced sleep efficiency and increased nocturnal wakefulness, likely mediated by inflammatory disruption of slow-wave sleep architecture (St-Onge et al. 2016). In contrast, unsaturated fats—particularly monounsaturated and PUFAs such as oleic acid and omega-3 PUFAs—exert beneficial effects on sleep. These effects are partly attributed to increased synthesis of lipid-derived mediators like prostaglandin D_2, which facilitate sleep onset through

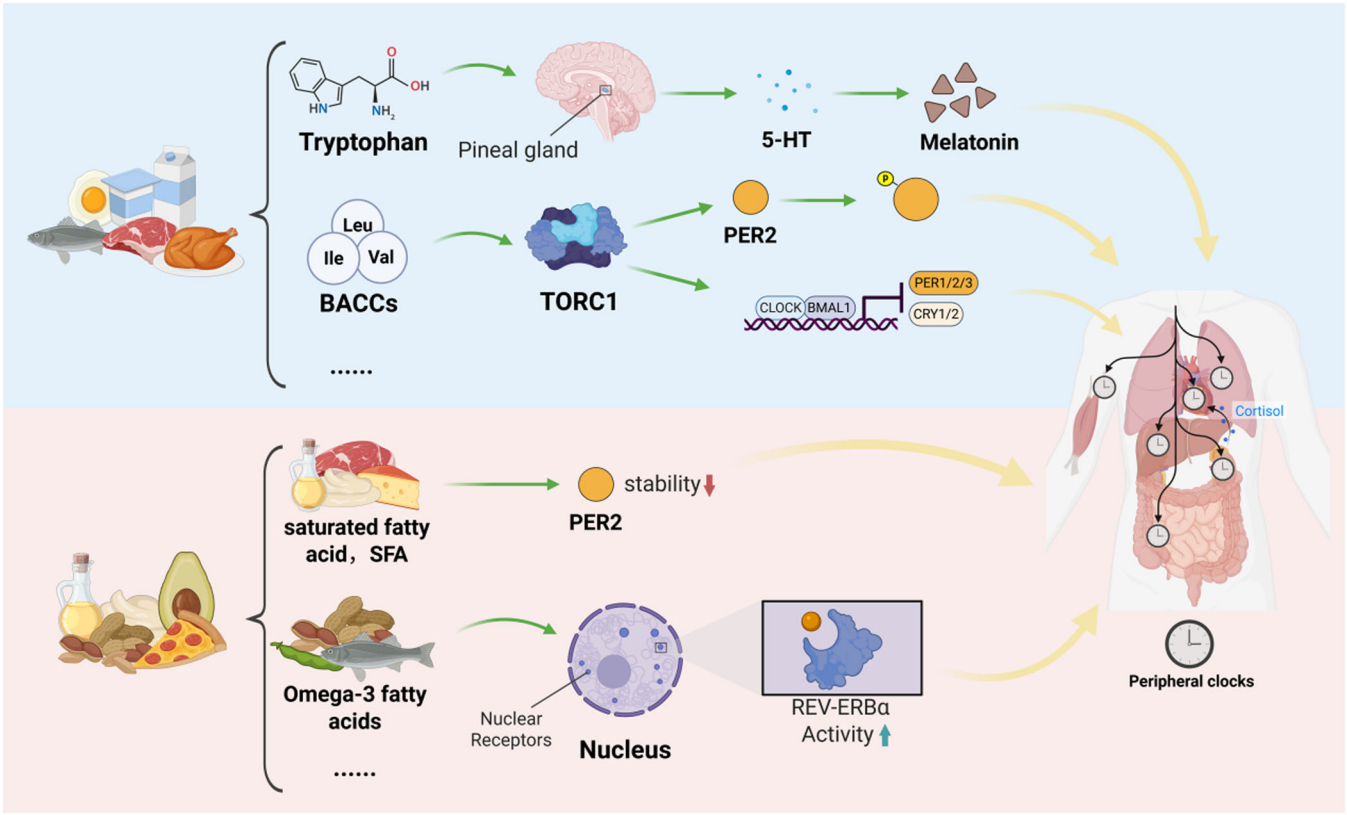

FIGURE 4 | Mechanisms through which dietary proteins and fats modulate circadian rhythms. Dietary tryptophan serves as a precursor for serotonin (5-HT) and melatonin synthesis in the pineal gland, thereby influencing central circadian signaling. Branched-chain amino acids (BCAAs) activate the mTORC1 complex, which phosphorylates PER2 and promotes its ubiquitin-mediated degradation, ultimately attenuating CLOCK:-BMAL1 transcriptional activity. Saturated fatty acids (SFAs) similarly destabilize PER2 protein, contributing to disrupted peripheral clock function. In contrast, omega-3 polyunsaturated fatty acids (PUFAs) enhance circadian rhythmicity by activating nuclear receptors such as REV-ERBα, which reinforce the expression of peripheral clock genes. These nutrient-responsive pathways converge on peripheral tissues (e.g., liver, muscle, gut) and may indirectly affect central clock output through hormonal mediators such as cortisol.

SCN-related pathways. Moreover, omega-3 fatty acids enhance the amplitude of *PER2* and *CRY1* rhythms in metabolic tissues by activating lipid-sensitive nuclear receptors such as PPARα.

Emerging evidence suggests that dietary fats interact with the gut microbiota to influence circadian physiology through the gut–brain axis. Omega-3 PUFAs promote microbial diversity and maintain the diurnal production of SCFAs, including butyrate and acetate, which peak during the active phase and activate G-protein coupled receptors (e.g., GPR43) in peripheral tissues and the pineal gland (Ding et al. 2022). These signals contribute to stable melatonin secretion and reinforce peripheral clock function. In contrast, HFDs disrupt microbial rhythmicity, lower SCFA production, and impair melatonin synthesis, exacerbating circadian misalignment.

Developmental stage also modifies the effects of high-fat intake on circadian function. Yan et al. (2022) showed that adolescent rodents exhibit greater sensitivity to HFD-induced circadian disruption compared to adults (Yan et al. 2022). This age-specific vulnerability is linked to differential activation of retinol metabolic pathways; during adolescence, elevated retinoic acid levels upregulate lipid synthesis genes such as *SREBP1*, while simultaneously destabilizing *REV-ERBα* expression. In adult animals, by contrast, HFDs predominantly disrupt ER stress-related pathways. These findings highlight the importance of age-tailored dietary strategies in preserving circadian homeostasis.

Fats also interact with other macronutrients to shape circadian outcomes. For instance, saturated fats impair insulin sensitivity, reducing the ability of carbohydrates to synchronize peripheral clocks via mTOR-mediated signaling (see Section 5.1). Conversely, combining omega-3 fatty acids with fiber-rich foods restores SCFA rhythmicity and reinforces *REV-ERBα*-dependent gene oscillations (Ding et al. 2022). Non-nutritional interventions such as light exposure and physical activity can further mitigate fat-induced circadian disruption: morning blue light enhances *BMAL1* expression in the SCN, while voluntary exercise activates AMPK in the liver, both contributing to realignment of metabolic rhythms (Bilu et al. 2022).

5.4 | Interactions Between Macronutrients and Circadian Rhythm

While individual macronutrients—carbohydrates, proteins, and fats—exert distinct effects on circadian physiology, their combined ingestion often produces synergistic or antagonistic outcomes through interconnected metabolic, hormonal, and

molecular pathways. These interactions modulate the expression of clock genes, hormonal oscillations, and sleep–wake regulation, underscoring the importance of evaluating nutrient combinations rather than isolated components.

A primary axis of macronutrient interaction involves carbohydrate–protein synergy in supporting peripheral clock function. Low-glycemic carbohydrates promote stable postprandial glucose levels, sustaining insulin-mediated activation of the PI3K/Akt pathway, which regulates PER2 phosphorylation and degradation (Barnea et al. 2009). Concurrently, dietary proteins supply tryptophan, a precursor to melatonin, and stimulate SIRT1 activity, which enhances circadian amplitude via deacetylation of BMAL1 and PER2 transcriptional complexes (Kent et al. 2022). When consumed together—especially in the morning—this combination optimally synchronizes hepatic clock gene oscillations through converging mTOR and insulin pathways. Conversely, evening intake of protein–carbohydrate meals may misalign circadian phase due to SCN-driven alterations in PER2 expression and reduced insulin sensitivity (Mendoza et al. 2010).

Antagonistic interactions are most evident in high-fat and high-sugar diets, which jointly disrupt circadian rhythmicity through overlapping and reinforcing mechanisms. Saturated fats impair PPARα signaling, thereby suppressing the transcription of lipid-metabolic and core clock genes such as *BMAL1* and *REV-ERBα* (Hatori et al. 2012; Kohsaka et al. 2007). Simultaneously, high-GI carbohydrates provoke abrupt insulin surges that accelerate PER2 degradation via the PI3K/Akt cascade, dampening rhythmic *CRY1* expression in the liver. These dual disruptions converge to blunt peripheral clock gene oscillations, promoting circadian misalignment and metabolic dysfunction.

Macronutrient interactions also influence sleep regulation, particularly through inflammatory and neurohormonal pathways. Diets combining monounsaturated fats with fiber-rich complex carbohydrates have been associated with improved slow-wave sleep, mediated by reduced NF-κB-driven inflammation and enhanced production of gut microbiota–derived SCFAs such as butyrate (St-Onge et al. 2016; Thaiss et al. 2014). SCFAs activate GPR43 receptors in the colon and pineal gland, reinforcing melatonin synthesis and stabilizing the onset of nocturnal rest. In contrast, combinations of saturated fats and low-protein intake impair sleep by reducing leptin rhythmicity and limiting tryptophan availability, both of which compromise melatonin signaling and promote fragmented sleep architecture (Lindseth et al. 2013).

At the hormonal level, nutrient combinations modulate circadian secretion profiles of melatonin and glucocorticoids. Carbohydrate–protein co-ingestion enhances melatonin production by increasing the plasma tryptophan/LNAA ratio (via insulin) and providing sufficient tryptophan precursor for serotonin conversion (Fernstrom 2013; Hartmann 1983). This effect is most pronounced when the meal is consumed 3–4 h before sleep, aligning with the circadian rise in pineal melatonin output. Conversely, diets rich in saturated fats and high-GI carbohydrates desynchronize corticosterone rhythms: fats delay its nocturnal peak by inhibiting REV-ERBα, while sugars blunt its early-morning surge by impairing cortisol–glucose feedback (Teeple et al. 2023). These combined effects contribute to HPA axis disruption and increased risk of metabolic syndrome.

TRF offers a practical model for examining how macronutrient composition interacts with feeding timing to affect circadian homeostasis. Evidence suggests that a TRF protocol incorporating moderate protein (20%–30%), low-GI carbohydrates (40%–50%), and unsaturated fats (20%–30%) optimally enhances circadian alignment. Protein promotes mTOR activation and peripheral clock synchronization during the feeding window (Deng et al. 2023), carbohydrates support stable glucose profiles and minimize PER2 degradation (Barnea et al. 2009), and unsaturated fats sustain REV-ERBα-regulated lipid metabolism oscillations (Hatori et al. 2012). In contrast, TRF regimens rich in saturated fats and simple sugars compromise circadian benefits by altering gut microbial rhythmicity, disrupting SCFA–SCN signaling, and impairing AMPK-mediated metabolic resetting (Ding et al. 2022).

6 | The Influence of Specific Nutrients and Food Components on Circadian Rhythm

6.1 | Dietary Fiber and Circadian Rhythm

Dietary fiber, a class of indigestible carbohydrates primarily fermented by gut microbiota, plays a pivotal role in shaping circadian rhythms through microbiota-derived metabolites, immune signaling, and nutrient–hormonal cross-talk. The rhythmic interaction between host and gut microbes is increasingly recognized as a crucial component of peripheral clock synchronization.

A primary mechanism by which fiber influences circadian biology is through the production of SCFAs, including butyrate, acetate, and propionate. These microbial fermentation products act as signaling molecules by activating G-protein–coupled receptors (GPR41 and GPR43) in peripheral tissues such as the liver, adipose, and colon. Butyrate, in particular, enhances *BMAL1* transcription by inhibiting histone deacetylases (HDACs), thereby increasing chromatin accessibility of core clock gene promoters (Fawad et al. 2022; Shon et al. 2024). Propionate complements this effect by stabilizing *PER2* protein via suppression of its ubiquitination, leading to strengthened circadian amplitude and phase consistency (Leone et al. 2015). Notably, colonic epithelial clocks are especially sensitive to these SCFAs. During the active feeding phase, fermentation of soluble fibers increases luminal SCFA levels, which upregulate *REV-ERBα* expression in colonocytes, aligning gut motility and barrier function with feeding behavior (Thaiss et al. 2014).

As illustrated in Figure 5, dietary fiber acts as a multifaceted circadian regulator by shaping microbial composition, enhancing SCFA production, and engaging metabolic, satiety-related, and immune pathways. These mechanisms converge on peripheral clocks across multiple tissues, underscoring the systemic impact of fiber–microbiota interactions on circadian homeostasis. High-fiber diets preserve diurnal oscillations in microbial composition: fiber-fermenting *Bacteroidetes* typically peak during the active/feeding phase, whereas *Firmicutes*—dominant during fasting—rise in the rest phase. In contrast,

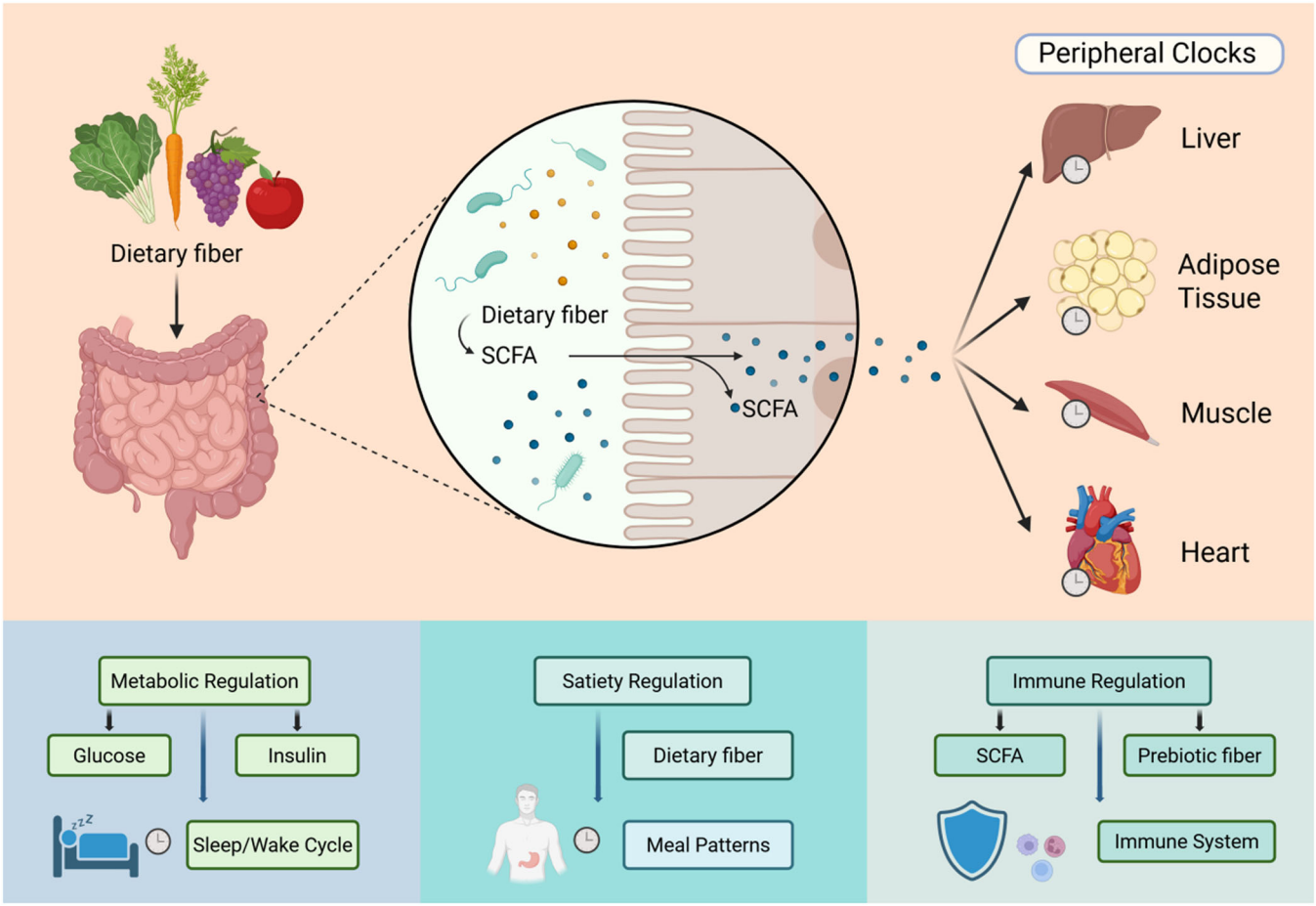

FIGURE 5 | Mechanisms by which dietary fiber regulates host circadian rhythms through gut-derived signals and systemic pathways. Dietary fiber is fermented by the gut microbiota to produce short-chain fatty acids (SCFAs), which influence peripheral clocks by modulating the expression of core clock genes in tissues such as liver, adipose, muscle, and heart. SCFAs also improve glucose homeostasis and insulin sensitivity, contributing to the stabilization of the sleep–wake cycle. Additionally, dietary fiber delays gastric emptying and, together with SCFAs, promotes satiety and helps entrain feeding patterns. On the immune front, SCFAs enhance intestinal barrier integrity and regulate immune cell function, while prebiotic fibers selectively support the growth of beneficial microbial species that influence immune circadian signaling. This multi-layered regulatory network underscores the role of dietary fiber as a zeitgeber that integrates metabolic, behavioral, and immune pathways to support circadian alignment.

low-fiber diets disrupt this temporal structure, leading to attenuated SCFA rhythmicity and subsequent desynchronization of peripheral clocks (De Filippo et al. 2010; Thaiss et al. 2014).

The anti-inflammatory properties of fiber-derived SCFAs also contribute to circadian homeostasis. Butyrate and propionate inhibit NF-κB signaling in intestinal immune cells and the hypothalamus, thereby reducing the production of pro-inflammatory cytokines such as IL-1β and Galectin-3—molecules known to suppress *BMAL1* expression and dampen sleep–wake rhythmicity (Cermakian et al. 2013; St-Onge et al. 2016). This anti-inflammatory effect extends to the central nervous system, where SCFAs modulate microglial activity, improving sleep efficiency and reducing nocturnal arousals.

Interactions between fiber and other macronutrients further shape circadian regulation. Soluble fiber delays glucose absorption from co-ingested carbohydrates, preventing insulin surges that would otherwise disrupt *PER2* rhythmicity in hepatic tissues (Barnea et al. 2009). When consumed alongside low-glycemic carbohydrates, fiber helps maintain stable postprandial glycemia and sustained SCFA production, synergistically enhancing *BMAL1* and *CRY1* oscillations. Additionally, co-ingestion of fiber and omega-3 fatty acids reinforces microbial rhythmicity: omega-3s promote the abundance of SCFA-producing bacteria such as *Faecalibacterium*, while fiber provides fermentable substrates, jointly increasing butyrate levels and stabilizing REV-ERBα–mediated lipid metabolism rhythms (Ding et al. 2022).

Fiber subtype also influences its chronobiological effects. Soluble fiber (e.g., from oats, psyllium) is efficiently fermented into SCFAs and acts directly on peripheral clocks. In contrast, insoluble fiber (e.g., from wheat bran) primarily contributes through its bulking effect and delay of gastric emptying, thereby reinforcing regular meal timing—a key external cue (zeitgeber) for circadian alignment (Howarth et al. 2001). Moreover, prebiotic fibers such as inulin and fructooligosaccharides selectively promote the growth of *Bifidobacteria* and *Lactobacilli*, which themselves exhibit robust diurnal oscillations. Their fermentation enhances SCFA levels particularly during the active phase, facilitating phase alignment between gut microbial activity and SCN-driven feeding rhythms (Swanson et al. 2020).

6.2 | Vitamins and Minerals Involved in Circadian Rhythm Regulation

Beyond the influence of dietary fiber and its fermentation products, micronutrients also play critical roles in tuning circadian machinery at the molecular level. Micronutrients influence the circadian system through diverse biochemical and cellular pathways, acting as cofactors, nuclear receptor ligands, ion channel modulators, and epigenetic regulators. These functions converge on the regulation of clock gene expression, hormone secretion, and sleep-wake physiology.

Vitamin B12 plays a key role in one-carbon metabolism by serving as a cofactor for methionine synthase, thereby sustaining levels of S-adenosylmethionine (SAM), a methyl donor essential for the rhythmic methylation of *PER2* and *CRY1* promoters in the SCN. Deficiency in vitamin B12 leads to reduced SAM availability, dampened *PER2* amplitude, and delayed melatonin onset, contributing to phase delays and impaired sleep efficiency (Okawa et al. 1998).

Vitamin D acts on the circadian system via its receptor (VDR), which is rhythmically expressed in the SCN and peripheral tissues. Upon activation, VDR can heterodimerize with BMAL1 and inhibit CLOCK/BMAL1-mediated transcription of *PER1*, modulating period length and amplitude. In states of vitamin D deficiency, this regulatory interaction is impaired, resulting in elevated *PER1* expression and lengthened circadian period. Moreover, low vitamin D increases pro-inflammatory cytokines such as TNF-α, which repress *BMAL1* expression through NF-κB signaling, further desynchronizing peripheral clocks (Bozkurt et al. 2012).

Magnesium contributes to circadian regulation by modulating NMDA receptor activity in SCN neurons. Adequate magnesium helps regulate calcium influx and supports the synchrony of neuronal oscillations. This synchrony is critical for robust *PER2* expression and consolidated sleep-wake rhythms. In contrast, magnesium deficiency disrupts NMDA-mediated glutamatergic signaling, leading to fragmented *PER2* expression and sleep disturbances (Abbasi et al. 2012; Dubocovich et al. 2010).

Zinc has been shown to stabilize CRY2 protein by preventing its ubiquitination and degradation via the FBXL3 pathway. This stabilization enhances the amplitude of the circadian negative feedback loop and promotes rhythmic gene expression in the liver and adipose tissue. Zinc deficiency reduces CRY2 stability, shortens the circadian period, and disrupts rhythmic glucose metabolism (Sato-Mito et al. 2011).

Iron also displays circadian dynamics in its absorption and physiological effects. The iron exporter ferroportin is rhythmically regulated by *PER2* in intestinal enterocytes, with expression peaking in the evening. This temporal alignment makes evening iron supplementation more effective, as it enhances systemic absorption and promotes synchronized *PER2/CRY1* expression in the liver (Dong et al. 2021). Additionally, brain iron is essential for tyrosine hydroxylase activity, and its deficiency reduces dopaminergic tone in the SCN, disrupting sleep-wake transitions and contributing to conditions such as restless legs syndrome (Allen et al. 2001; Earley et al. 2000).

Beyond their individual roles, micronutrients often interact to influence circadian regulation synergistically. For example, vitamin B6 and magnesium cooperatively promote melatonin synthesis: vitamin B6 facilitates the conversion of tryptophan to serotonin, while magnesium enhances serotonin uptake into pinealocytes, where it is further converted to melatonin (Abbasi et al. 2012; Richard et al. 2009). Similarly, vitamin D and iron interact in immune-circadian coordination. VDR upregulates ferroportin in macrophages, promoting iron release that aligns with the diurnal peaks of immune activity (Farrell et al. 2023; Santos et al. 2023).

6.3 | Phytochemicals and Their Effects on Circadian Rhythm

Plant-derived bioactives modulate the circadian system through three complementary avenues—(1) direct binding to nuclear receptors or kinases that gate the *CLOCK/BMAL1* feedback loop, (2) interaction with nutrient-sensing pathways such as SIRT1 and AMPK, and (3) remodeling of gut-derived metabolites (SCFAs, secondary bile acids) that relay timing cues to peripheral clocks. Below, the main chemical classes are described in one continuum to preserve the logical flow of mechanisms, rather than as isolated sub-sections.

Flavonoids constitute the most intensively studied class. Nobiletin, a polymethoxylated flavone abundant in citrus peel, docks to the ligand-binding domain of retinoic-acid-related orphan receptor-α (RORα). RORα then co-activates the *BMAL1* promoter, amplifying BMAL1 protein and, downstream, elevating *PER2* oscillation amplitude in liver and muscle; the enhanced oscillatory strength synchronizes lipid-oxidation genes such as *PPARα* and *CPT1a* and improves glucose tolerance (He et al. 2016). Polymethoxyflavones from black ginger operate through another node: they allosterically inhibit casein-kinase-1δ, slowing PER protein phosphorylation and degradation, thereby lengthening PER half-life and restoring 24 h periodicity in HFD models (Yoshida et al. 2023).

Other polyphenols interface with the nutrient-sensing arm of the clock. Resveratrol directly activates SIRT1; SIRT1 deacetylates both BMAL1 and PER2, reinforcing the robustness of their transcriptional cycles and re-establishing rhythmic GLUT4 translocation in skeletal muscle, which underlies its insulin-sensitizing action (Um et al. 2007). Curcumin predominantly targets AMPK; AMPK-mediated phosphorylation of CRY1 accelerates its proteasomal turnover, facilitating phase-advancement of peripheral clocks during metabolic resetting, a property exploited to reverse high-fat-diet blunting of hepatic *PER2* (Auld et al. 2017).

Alkaloids and other specialized metabolites connect the gut microbiota to clock machinery. Piperine reverses obesity-induced arrhythmia by restoring the diurnal *Firmicutes*-to-*Bacteroidetes* ratio and boosting nocturnal butyrate production. Butyrate activates hepatic GPR43, which in turn upregulates *REV-ERBα* and realigns lipid catabolism genes with circadian timing (Zhang et al. 2024). Theabrownin—a high-molecular-weight polyphenolic fraction in Pu-erh tea—suppresses

bacterial 7α-dehydroxylase, lowering serum secondary bile acids and re-establishing the rhythmic activation of farnesoid-X-receptor (FXR); FXR is a transcriptional enhancer of *BMAL1* in liver and adipose tissue, thus synchronizing systemic metabolism with SCN cues (Zhao et al. 2025). Sulforaphane acts centrally and peripherally: NRF2 activation in the hypothalamus elevates *PER2* expression and strengthens SCN output, while concomitantly lowering hepatic *CRY1* via antioxidant-responsive elements, thereby sharpening central–peripheral phase coherence (He et al. 2024).

Network-level synergies accentuate these single-compound effects. Soluble dietary fiber supplies fermentable substrates that intensify butyrate-mediated *REV-ERBα* signaling, amplifying the clock-enhancing actions of quercetin and other flavonoids. Conversely, omega-3 polyunsaturated fats heighten SIRT1 activity, potentiating resveratrol-induced BMAL1 deacetylation and further enlarging oscillation amplitude in muscle clocks—an interclass cooperation that mirrors the macronutrient interactions outlined in Section 5.3.

In circadian metrics, most phytochemicals converge on: (i) amplitude expansion (e.g., nobiletin, resveratrol), (ii) controlled phase-shifting (curcumin, sulforaphane), or (iii) period stabilization (black-ginger polymethoxyflavones). By targeting complementary nodes—nuclear receptors, post-translational modifiers, microbial metabolites—they offer a multidimensional toolkit for chrono-nutrition strategies aimed at reinforcing endogenous rhythms without pharmacological side-effects. Collectively, these bioactive compounds not only provide mechanistic insights into diet–circadian interactions but also present promising dietary interventions to enhance circadian health, bridging basic research with practical nutritional strategies.

6.4 | Caffeine, Alcohol, and Other Dietary Components Impacting Circadian Rhythm

Caffeine, alcohol, and other dietary components can have a significant impact on circadian rhythm regulation.

Caffeine is the most widely consumed psychoactive compound, and its chronobiological effects arise from a dual action on the central pacemaker and on peripheral clocks. By antagonizing adenosine A_1/A_2A receptors in the hypothalamus, evening caffeine intake blocks adenosine-mediated inhibition of wake-promoting neurons and delays the SCN-driven rise in melatonin. This produces a 40- to 60-min phase delay in *PER1*/*PER2* expression in the SCN and reduces the amplitude of the cortisol rhythm by approximately 20% (Burke et al. 2015; Wright et al. 2015). Long-term exposure elicits an additional, SCN-independent pathway: caffeine potentiates striatal dopamine release, and sustained dopaminergic signaling shifts *CRY1* and *BMAL1* oscillations in skeletal muscle and liver, leading to persistent behavioral and metabolic desynchrony even under constant-light conditions (Tahara et al. 2024). Timing is critical; doses ingested after 15:00—when caffeine's 3–5 h half-life overlaps with the SCN's pre-melatonin window—significantly prolong sleep latency and lower sleep efficiency compared with morning consumption.

Alcohol exerts a biphasic perturbation of circadian organization. Acutely, ethanol enhances GABAergic neurotransmission, producing transient drowsiness, but subsequently fragments sleep by suppressing REM—a stage that consolidates SCN rhythmic output. These rapid changes dampen *BMAL1* oscillation amplitude within the SCN and blunt the nocturnal melatonin surge (Chen et al. 2006). Chronic intake amplifies disruption: persistent ethanol exposure downregulates pineal *N*-acetyl-transferase, flattening melatonin rhythms, while simultaneously upregulating hepatic REV-ERBα expression, thereby uncoupling lipid-metabolic gene rhythms from central timing. Epigenetic hyper-methylation of *PER2* and *CLOCK* promoters sustains these defects long after abstinence (Spanagel et al. 2005). Clinically, this shift moves the daily peak of hepatic gluconeogenesis from predawn to midnight, predisposing heavy drinkers to fasting hyperglycaemia and dyslipidaemia.

Other bioactive compounds further illustrate tissue-specific entrainment. Capsaicin activates TRPV1 channels in enteroendocrine cells, initiating vagal-afferent signaling to the hypothalamus; in rodents this advances hepatic *PER1*/*BMAL1* phase by approximately 1 h, tightening alignment between nutrient influx and hepatic metabolism (Iwamoto et al. 2014). Ω-3 poly-unsaturated fatty acids counteract alcohol-induced misalignment by activating hypothalamic SIRT1; enhanced deacetylation stabilizes BMAL1 and restores SCN neuronal synchrony, partly explaining improved sleep quality in moderate drinkers who consume EPA/DHA-rich diets (Mocking et al. 2013; Mukherji et al. 2015).

Interactions among compounds compound circadian stressors. Co-ingestion of caffeine and alcohol—a common practice in mixed drinks—masks alcohol's sedative phase signal while preserving caffeine-driven arousal. Bedtime is thereby postponed beyond the SCN-defined "biological night," widening the phase gap between central and peripheral oscillators; in human studies this translates into exaggerated post-prandial hyper-glycaemia the following morning owing to desynchronised hepatic *GLUT2* rhythms (Burke et al. 2015; Roehrs and Roth 2001).

Quantitatively, these compounds modulate two core circadian parameters: phase (e.g., caffeine delays melatonin onset and *PER* expression; alcohol advances sleep onset but delays REM consolidation) and amplitude (e.g., caffeine reduces cortisol oscillation; chronic alcohol suppresses the oscillatory amplitude ofmelatonin and *BMAL1* rhythms). Their tissue-specific molecular targets—adenosine and dopamine receptors, GABAergic circuits, TRPV1, SIRT1, REV-ERBα—connect environmental exposure to clock-gene transcriptional feedback, offering mechanistic touchpoints for chrono-nutritional or pharmacological intervention.

7 | Strategies to Optimize Circadian Rhythm Through Diet

7.1 | Meal Planning and Timing Recommendations

Effective meal planning serves as a practical strategy to reinforce circadian alignment by modulating peripheral clocks through nutritional and temporal cues. This section integrates

current evidence to provide time-specific dietary recommendations grounded in circadian physiology.

7.1.1 | Synchronizing Meals With Circadian Phases

The synchronization of food intake with circadian phases is essential for aligning metabolic signals with the endogenous biological clock. Regular meal timing entrains peripheral clocks—especially in the liver, pancreas, and gastrointestinal tract—by stabilizing the rhythmic expression of core clock genes such as *BMAL1* and *PER2* (Damiola et al. 2000). Consistent eating schedules reinforce temporal signals, particularly through nutrient-sensing pathways like AMPK and mTOR, thereby promoting metabolic homeostasis and reducing variability in hormonal secretion (Lamia et al. 2009).

7.1.2 | Optimal Meal Timing Strategy

Breakfast should be consumed within 1–2 h after waking, coinciding with the morning cortisol peak and the circadian elevation of insulin sensitivity (Farshchi et al. 2005; Sutton et al. 2018). A protein- and fiber-rich breakfast enhances GLP-1 and leptin signaling, while suppressing postprandial glucose excursions and reinforcing hepatic *REV-ERBα* expression, thereby supporting synchronized thermogenesis and appetite regulation (Basolo et al. 2021; Jakubowicz et al. 2013).

Lunch is ideally timed 4–6 h after breakfast, during the mid-active phase when nutrient absorption and mTOR activity are elevated. Prioritizing complex carbohydrates and lean protein at this time promotes sustained energy release and optimal anabolic responses (Rutters et al. 2014).

Dinner should be completed at least 2–3 h before habitual bedtime, preferably before 19:00. Late-evening eating disrupts melatonin onset, delays *PER1* expression, and induces phase misalignment in peripheral tissues, particularly the liver and adipose tissue (Gooley et al. 2011; Petersen et al. 2022). Minimizing caloric load and GI during dinner helps mitigate these effects.

7.1.3 | Food Composition Based on Time of Day

Temporal specificity in macronutrient distribution supports circadian entrainment:

Morning: Emphasize low-GI carbohydrates and high-quality proteins to activate mTOR and SIRT1 signaling, reinforce clock gene amplitude, and enhance morning alertness (Fernstrom 2013; Um et al. 2007).

Afternoon: Balanced intake of carbohydrates and fats supports stable energy levels while sustaining peripheral clock coherence through ongoing nutrient sensing (Kohsaka et al. 2007).

Evening: Favor light, low-fat, and protein-moderate meals. Avoid excessive protein and carbohydrate co-ingestion, which may impair nocturnal melatonin synthesis and alter hepatic glucose regulation (Crönlein et al. 2013; Sato et al. 2011).

7.1.4 | Avoiding Mistimed Eating and Stimulants

Mistimed or irregular eating patterns—such as frequent late-night snacking or skipped breakfast—are associated with circadian misalignment and adverse metabolic outcomes, including insulin resistance, dyslipidemia, and increased adiposity (Gonnissen et al. 2012; McHill et al. 2017). Similarly, the consumption of stimulants should be temporally regulated:

Caffeine intake after 15:00 delays melatonin onset and impairs sleep quality by inhibiting adenosine signaling and altering SCN-driven *PER* gene rhythms (Burke et al. 2015).

Alcohol, particularly when consumed in the evening, disrupts REM sleep and suppresses nocturnal *BMAL1* expression, leading to reduced circadian amplitude (Chen et al. 2006; Spanagel et al. 2005).

Adherence to an eTRF protocol—such as an 8 a.m. to 4 p.m. eating window—has been shown to improve circadian alignment, enhance insulin sensitivity, and restore rhythmic expression of metabolic genes (Hatori et al. 2012; Sutton et al. 2018). This approach leverages both feeding–fasting cycles and the body's intrinsic rhythms to optimize metabolic outcomes.

7.2 | Macronutrient Distribution for Circadian Rhythm Optimization

While the timing of meals is a key determinant of circadian alignment, the distribution of macronutrients across the day further refines metabolic and clock gene responses. The temporal distribution of macronutrients—carbohydrates, proteins, and fats—exerts a profound influence on the circadian system. This section outlines chrono-nutritional strategies for aligning macronutrient intake with endogenous metabolic rhythms to enhance physiological outcomes, guided by evidence from nutrient-sensing pathways, hormonal oscillations, and clock gene dynamics.

7.2.1 | Carbohydrates: Timing and Glycemic Load

Carbohydrate intake should be front-loaded during the day to synchronize with circadian peaks in insulin sensitivity, GLUT4 translocation, and β-cell responsiveness. Morning ingestion of low-GI carbohydrates promotes stable postprandial glycemia, activates the mTOR–PER2 pathway, and preserves rhythmic expression of *BMAL1* and *CLOCK* in hepatic and adipose tissues (Barnea et al. 2009; Um et al. 2007). Additionally, carbohydrate-induced insulin secretion facilitates tryptophan uptake into the brain, enhancing serotonin and subsequent melatonin synthesis when timed appropriately (Fernstrom 2013).

In contrast, evening carbohydrate consumption—particularly high-GI forms—induces postprandial hyperglycemia and suppresses nocturnal melatonin, thereby delaying *PER2* and *CRY1* expression and impairing sleep quality (Afaghi et al. 2007; Gooley et al. 2011). Thus, minimizing

carbohydrate intake after 18:00 supports metabolic alignment and circadian coherence.

7.2.2 | Proteins: Temporal Anabolic Responsiveness

Protein intake exerts circadian phase–dependent effects on muscle protein synthesis, satiety signaling, and clock gene regulation. Morning and midday ingestion of high-quality protein (especially rich in leucine and other branched-chain amino acids) coincides with peak mTORC1 activity, enhancing phosphorylation and degradation of PER2, a mechanism that strengthens peripheral clock amplitude (Deng et al. 2023; Um et al. 2007).

Distributed protein intake across three meals—rather than skewing toward evening—optimizes amino acid utilization and avoids nocturnal stimulation of gluconeogenesis and sympathetic tone, which may disrupt SCN-mediated sleep signaling (Crönlein et al. 2013). Co-ingestion with complex carbohydrates in the early active phase further potentiates insulin-mediated amino acid uptake and supports alignment of feeding and anabolic rhythms.

7.2.3 | Fats: Composition and Chronobiological Effects

The type and timing of fat consumption modulate peripheral clock gene oscillations, inflammatory tone, and energy metabolism. Saturated fats, particularly when consumed late in the day, suppress nuclear receptors such as PPARα and REV-ERBα, disrupting lipid metabolic rhythms and blunting *BMAL1* and *PER2* expression in the liver and adipose tissue (Hatori et al. 2012; Kohsaka et al. 2007).

In contrast, monounsaturated and polyunsaturated fats—especially omega-3 fatty acids like EPA and DHA—promote peripheral clock robustness by activating lipid-sensitive transcription factors and enhancing SCFA-mediated gut–brain signaling (Ding et al. 2022). Incorporating unsaturated fats earlier in the day improves lipid oxidation timing and supports circadian regulation of appetite and sleep.

7.2.4 | Integrative Macronutrient Strategies

Chrononutritional alignment requires coordinated macronutrient distribution across the day:

Breakfast (within 1–2 h of waking): Prioritize low-GI carbohydrates, moderate protein (20–25 g), and unsaturated fats to initiate metabolic phase resetting and promote satiety.

Lunch (4–6 h after breakfast): Maintain balanced intake of all macronutrients to support sustained energy and reinforce peripheral oscillations through converging mTOR and insulin signaling.

Dinner (at least 2–3 h before sleep): Favor light meals with low carbohydrate and saturated fat content to minimize metabolic load during the rest phase and avoid interference with melatonin secretion and *REV-ERBα*–mediated lipid metabolism.

For individuals practicing TRF, macronutrient quality becomes critical. Protocols that combine early feeding windows (e.g., 8 a.m. to 4 p.m.) with nutrient profiles rich in fiber, lean proteins, and unsaturated fats have been shown to preserve circadian amplitude, enhance metabolic flexibility, and restore hormonal rhythmicity (Hatori et al. 2012; Sutton et al. 2018).

7.3 | Incorporating Specific Nutrients and Food Components for Circadian Health

A growing body of chrono-nutritional research highlights discrete nutrients and bioactive compounds that interact with the molecular clock, sleep–wake regulation, and peripheral metabolic rhythms. This section groups those factors by their primary mechanistic targets and offers time-of-day recommendations that complement the macronutrient strategies outlined in Sections 7.1 and 7.2.

7.3.1 | Nutrients That Modulate Clock-Gene Expression

7.3.1.1 | SCFA Precursors—Dietary Fiber. Soluble fibers (e.g., inulin, β-glucan) are fermented into butyrate, propionate and acetate. Butyrate activates G-protein-coupled receptors GPR41/GPR43 and inhibits HDACs, thereby enhancing chromatin accessibility at the *BMAL1* promoter and strengthening circadian amplitude in hepatocytes and colonocytes (Gasaly et al. 2021). Evening SCFA peaks generated by a high-fiber lunch align intestinal clock output with the forthcoming rest phase.

7.3.1.2 | Polyunsaturated Fatty Acids. Marine ω-3 PUFAs (EPA, DHA) bind PPARα and increase hepatic *PER2* amplitude, while also upregulating REV-ERBα to tighten lipid-gene oscillations and reduce inflammatory NF-κB signaling (Ding et al. 2022). Consuming oily fish or algal oils at breakfast synergizes with morning cortisol to promote lipid oxidation during the active phase.

7.3.1.3 | Clock-Sensitizing Phytochemicals. Nobiletin docks to RORα, driving *BMAL1* transcription and rescuing high-fat-diet–induced clock damping; early-day ingestion maximizes its phase-advancing effect (He et al. 2016).

Resveratrol activates SIRT1, de-acetylating BMAL1/PER2 and restoring rhythmic GLUT4 translocation in skeletal muscle (Um et al. 2007).

Sulforaphane triggers Nrf2 signaling, elevating hypothalamic *PER2* while lowering hepatic *CRY1*, thereby sharpening central–peripheral phase coherence (He et al. 2024).

7.3.2 | Nutrients That Influence Sleep–Wake Regulation

Tryptophan-rich proteins (turkey, tofu, dairy) increase the plasma Trp/LNAA ratio when co-ingested with low-GI carbohydrate at dinner (approximately 3 h before bedtime). This supports serotonin and subsequent melatonin synthesis without

provoking nocturnal hyperglycaemia (Amaral et al. 2014; Crönlein et al. 2013).

Magnesium and vitamin B6 cooperate in the serotonin–melatonin pathway. Magnesium modulates SCN NMDA-receptor calcium flux, stabilizing *PER2* neuronal firing, while B6 is a co-factor for aromatic-L-amino-acid decarboxylase (Abbasi et al. 2012; Richard et al. 2009). Evening inclusion of leafy greens plus whole-grain cereals supplies both.

7.3.3 | Nutrients That Support Peripheral Clock Synchronization

Iron (time-specific absorption)—ferroportin peaks in the early evening under *PER2* control; moderate iron-rich snacks (e.g., roasted chickpeas) at that time optimize uptake and preserve hepatic *CRY1* rhythmicity (Dong et al. 2021).

Pre-/pro-biotics—inulin and bifidogenic strains (e.g., *Bifidobacterium longum*) amplify diurnal SCFA production, reinforcing REV-ERBα signaling in adipose tissue and attenuating diet-induced obesity (Thaiss et al. 2014).

7.3.3.1 | Synergistic Combinations. Fiber + ω-3 PUFAs elevate butyrate and enhance REV-ERBα activity more than either alone, while resveratrol potentiates SIRT1-dependent effects of fasting within time-restricted-feeding (TRF) protocols (Hatori et al. 2012).

7.3.4 | Dietary Components That Should Be Moderated

Stimulants and xenobiotics discussed extensively in Section 6.4 (e.g., caffeine, alcohol) attenuate melatonin or disrupt *BMAL1* amplitude when consumed outside the biological day. To preserve the benefits of the nutrients above, limit stimulant intake to the early active phase and minimize evening exposure to ultra-processed foods high in saturated fat and added sugars, which suppress PPARα and accelerate PER2 degradation (Kohsaka et al. 2007).

7.4 | Considerations for Special Populations (e.g., Shift Workers, Athletes)

While general chrono-nutritional principles support circadian health in most individuals, certain populations—such as shift workers, athletes, and older adults—exhibit altered circadian dynamics and metabolic demands. This section offers targeted dietary strategies tailored to their physiological contexts, emphasizing time-specific nutrient intake and circadian re-alignment.

7.4.1 | Shift Workers

Shift workers experience chronic circadian misalignment due to light exposure at night and mistimed food intake, leading to increased risks of metabolic syndrome, insulin resistance, and disrupted sleep (Kecklund and Axelsson 2016). To mitigate these effects:

Anchor food intake during the biological day: Whenever possible, confine eating to daytime hours, even during night shifts. A modified TRF window (e.g., 08:00–18:00) maintains coherence of hepatic and adipose peripheral clocks via synchronized *PER2* and *BMAL1* expression (Petersen et al. 2022).

Avoid late-night meals: Consuming food during the biological night induces phase shifts in peripheral clocks while the SCN remains light-entrained, causing internal desynchrony and impairing glucose tolerance (Damiola et al. 2000).

Use caffeine strategically: Limit caffeine intake to the early part of the waking period (approximately first 6 h) and avoid consumption within 8 h of desired sleep onset. Combined with 2500–3000 lux bright light, morning caffeine can phase-delay the circadian clock, improving wakefulness during nocturnal work (Burke et al. 2015).

Rehydrate with low-glycemic, electrolyte-rich fluids: Nighttime sugar-sweetened beverages may disrupt hepatic *REV-ERBα* and *GLUT2* oscillations, worsening metabolic outcomes (Sato et al. 2011).

7.4.2 | Athletes

Athletes face distinct challenges due to exercise-induced metabolic shifts, variable training times, and the need for efficient recovery. Circadian-timed nutrition can improve performance, recovery, and sleep quality.

Pre-exercise nutrition: For morning training, consume a small low-fat, carbohydrate-rich meal 60–90 min before exercise to leverage circadian peaks in glycolytic enzyme activity and insulin sensitivity (Edinburgh et al. 2020).

For late-day training or competition, ensure a carbohydrate-dense lunch to load glycogen stores while avoiding heavy pre-exercise meals in the evening that could impair melatonin synthesis.

Post-exercise intake: Morning sessions: Prioritize carbohydrate repletion (1–1.2 g/kg) with 20–30 g high-leucine protein to activate mTOR and support *PER2*-regulated anabolic signaling.

Evening sessions: Emphasize protein-dominant recovery (0.4 g/kg), limiting simple carbohydrates to avoid suppression of melatonin and phase delay of sleep-related *BMAL1* expression (Crönlein et al. 2013; Rutters et al. 2014).

Evening recovery: Consider a bedtime snack containing tryptophan, magnesium, and vitamin B6 (e.g., yogurt with oats and banana) to promote serotonin–melatonin conversion and support sleep onset (Richard et al. 2009).

7.4.3 | Older Adults

Aging is associated with attenuated circadian amplitude, reduced melatonin secretion, and impaired anabolic sensitivity.

Nutritional strategies can reinforce oscillatory strength and support metabolic resilience:

Protein timing and quality: Older adults require higher leucine-rich protein intake in the morning (≥ 0.4 g/kg) to compensate for blunted mTOR activation and muscle protein synthesis rhythms (Deng et al. 2023).

Support melatonin rhythms: Evening meals should be light, low in fat, and supplemented with tryptophan and magnesium to enhance melatonin biosynthesis and promote sleep consolidation (Abbasi et al. 2012).

7.4.4 | Individuals With Metabolic Disorders

People with impaired glucose tolerance, insulin resistance, or obesity benefit from more aggressive circadian alignment strategies:

Adopt eTRF: Limiting intake to the early part of the day (e.g., 08:00–16:00) enhances insulin sensitivity, preserves circadian gene expression, and reduces hepatic lipogenesis (Sutton et al. 2018).

Front-load caloric intake: Distribute approximately 40% of daily calories at breakfast, 35% at lunch, and $\leq 25\%$ at dinner. This aligns with circadian peaks in insulin secretion and nutrient absorption, improving glycemic and lipid profiles (Jakubowicz et al. 2013).

Focus on nutrient synergy: Combine low-GI carbohydrates, dietary fiber, and ω-3 PUFAs to reinforce *PER2* and *REV-ERBα* rhythms, reduce inflammation, and improve hormonal regulation of appetite and energy metabolism (Barnea et al. 2009; Ding et al. 2022).

8 | Conclusion

Circadian rhythms orchestrate a wide array of physiological processes, from sleep–wake cycles to metabolic regulation, through an intricate network of central and peripheral clocks. While light remains the principal synchronizer of the central pacemaker in the SCN, emerging evidence highlights the powerful role of food intake as a zeitgeber for peripheral clocks, particularly in metabolically active tissues such as the liver, adipose tissue, and skeletal muscle. Disruption of the temporal relationship between feeding behavior and internal circadian timing has been consistently linked to adverse health outcomes, including metabolic syndrome, obesity, insulin resistance, and impaired sleep.

This review provides a comprehensive synthesis of current findings on how both the timing and composition of food intake affect circadian physiology. At the molecular level, nutrient-sensing pathways—such as AMPK, mTOR, and SIRT1—integrate dietary cues into clock gene regulation, enabling dynamic alignment between metabolism and environmental rhythms. Specific macronutrients and micronutrients, along with bioactive compounds like flavonoids and SCFA precursors, modulate clock function via distinct but interconnected mechanisms, including nuclear receptor activation, post-translational modification, and gut microbiota–mediated signaling.

Beyond mechanistic insights, we underscore the translational potential of chrono-nutritional strategies. Meal timing, macronutrient distribution, and the incorporation of clock-targeting nutrients can be strategically employed to reinforce circadian alignment and improve metabolic outcomes. Particularly, eTRF, front-loaded carbohydrate and protein intake, and avoidance of late-night high-fat or stimulant consumption offer practical and evidence-based interventions.

Nonetheless, several knowledge gaps remain. Individual variability in circadian responsiveness, gene–diet interactions, and the long-term efficacy of chrono-nutrition in diverse populations warrant further investigation. Future research should aim to integrate circadian biomarkers, wearable technologies, and personalized nutrition frameworks to refine and implement circadian-friendly dietary guidelines in clinical and public health settings.

In conclusion, aligning dietary behaviors with circadian biology represents a promising frontier in preventive nutrition and metabolic health. By bridging molecular chronobiology and practical dietary guidance, chrono-nutrition holds the potential to restore internal rhythmicity and promote holistic well-being in modern societies increasingly prone to circadian disruption.

Author Contributions

Jiazheng Hu: conceptualization, writing – review and editing, writing – original draft, methodology, software, data curation, visualization. **Hongyu Ye:** writing – review and editing, writing – original draft, conceptualization, methodology, software, data curation, visualization. **Mengxin Wang:** writing – original draft, writing – review and editing, conceptualization, methodology, software, data curation, visualization. **Han Yang:** formal analysis, validation, investigation. **Manxi Wu:** formal analysis, validation, investigation. **Jinping Cao:** formal analysis, validation, investigation, methodology, supervision, funding acquisition, project administration. **Chongde Sun:** methodology, supervision, formal analysis, project administration, validation, investigation, funding acquisition, resources. **Yue Wang:** methodology, validation, investigation, funding acquisition, formal analysis, project administration, supervision, resources.

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Ethics Statement

This study does not involve studies on human embryos or fetuses (including human embryonic stem cells), recombinant DNA technology, empirical studies or medical trials with human subjects, acquisition or use of human cells and tissues, or animal experiments or medical research on animals. All research activities comply strictly with international ethical guidelines and national laws and regulations, ensuring no involvement in ethically sensitive areas.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the article or from the corresponding author upon reasonable request.

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