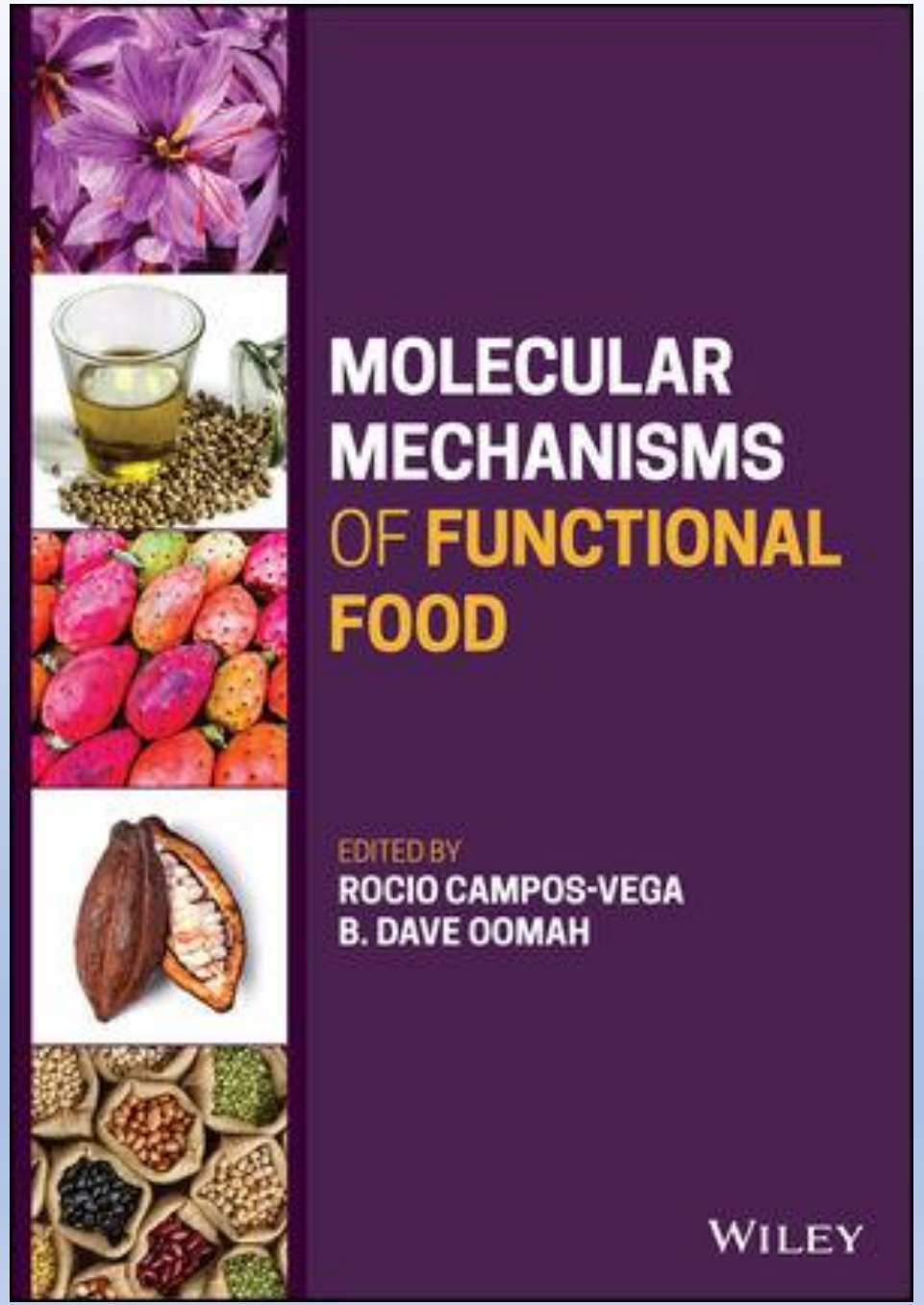

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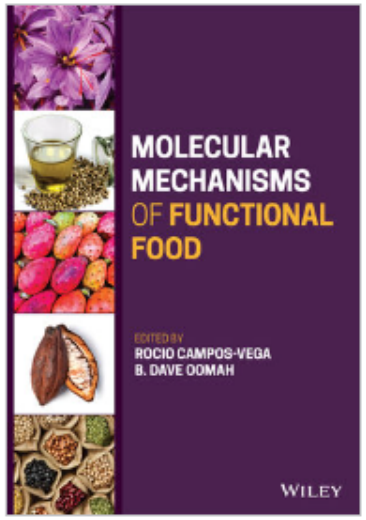

Molecular Mechanisms of Functional Food

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Molecular Mechanisms of Chronobiotics as Functional Foods

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3.1 Introduction

The establishment of *chrononutrition* as an emerging topic within *chronobiology* has a peculiar history. Empirical observations on rhythmic "sunrise to sunset" patterns in living organisms, the object of study in *chronobiology* (a.k.a. *circadian biology*), comes from the Hippocratic era, the term desynchronosis and its relationship of environmental light and temperature with sleep patterns date from the fifties (Folk Jr, 1957). The first review on chronobiology indexed in Scopus appeared in 1920 (Halberg, 1969). Jürgen Aschoff and Collin Pittendrigh are considered the fathers of modern chronobiology with their pioneering work on the natural entrainment (synchronization) of circadian (circa "around" or "approximately", diem "day") systems, derived from their so-called "resonance" and "bunker" experiments (Daan, 2000). Konopka and Benzer (1971) were perhaps the first to report that certain genes located in the X chromosome controls the timekeeping system in *D. melanogaster*, while the CLOCK (*circadian locomotor output cycles protein kaput*) gene reported by Takahashi in 1997 is one of the circadian genes controlling a plethora of physiological process (including the sleep–wake cycle) in mammals (Semenova, Madaeva, & Kolesnikova, 2021). However, the 2017 Nobel Prize in Physiology or Medicine was jointly awarded to Jeffrey Hall, Michael Rosbash, and Michael Young for their work on the mechanism underlying the circadian rhythm. Concurrently to modern chronobiology, chrononutrition was also leaving its mark. The scientific basis of modern chrononutrition (Dufoo-Hurtado, Wall-Medrano, & Campos-Vega, 2020; Halberg, 1989) is based on the biological periodicity of liver glycogen deposition and/or changes in body temperature in birds, humans, and other mammals (Ågren, Wilander, & Jorpes, 1931; Higgins & Mann, 1926), the body core temperature altered by starvation and *MESOR* (*Midline Estimating Statistic of Rhythm*) (Nelson & Halberg, 1986) and the role of dietary tryptophan (Trp) as a synchronizer of the circadian rhythm with external zeitgebers (environmental cues) (Wurtman, Shoemaker, Larin and Rosenthal, 1968). Although the use of the term

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Table 3.1 Advances in scientific publication on chronobiology, chrononutrition, and chronobiotics.

Year	Chronobiology	Chronobiotic	Chrononutrition
1900–1959	20	0	0
1960–1969	37	0	0
1970–1979	840	26	0
1980–1989	2630	41	3
1990–1999	5100	271	6
2000–2009	11400	1080	76
2010–2019	18300	2030	887
2020–2021*	5380	411	455

*Publications as of June 2021.
Source: Google scholar.

chronobiotic began in the seventies for drugs with chronotypic effect such as pentobarbital and theophylline–a green coffee bioactive (Ehret, Potter, & Dobra, 1975), the term chrononutrition appeared in scientific publications from 1980 onward (Table 3.1) and formal Japanese textbooks between 2005 and 2009 (Oda, 2015).

The body's circadian system consists of the central (SCN) and peripheral (organs) clocks that allow metabolic, physiological, and behavioral functions to oscillate between daylight and darkness (Ba-Ali et al., 2019). Such rhythmicity avoids the concurrence of conflicting behaviors (e.g. hunger vs. sleep) and cellular homeostasis (e.g. anabolic vs. catabolic processes), reducing the odds for metabolic disturbances (Challet, 2015; Plano et al., 2017). Chronodisruption should actually be considered bidirectional since wake–sleep cycles are severely disrupted by diseases affecting cytoplasmic homeostasis (Beesley et al., 2020). Also, the food anticipatory activity (FAA) attributed to the food-entrainable oscillator located outside the SCN precede circadian responses such as gene expression, enzyme secretion, hormone release, and afferent signals necessary for gastrointestinal digestion, nutrients bioconversion, and absorption before feeding (Shibata, Hirao, & Tahara, 2010). Chrononutrition has a remarkable translational, clinical, and therapeutic potential in regulating the circadian rhythm by modifying dietary patterns (e.g. timing and diet quality) and promoting the intake of chronobiotics such as phytomelatonin, prebiotics, glucose, amino acids, alcohol, retinoic acid, and short-chain fatty acids (SCFAs) (Dufoo-Hurtado, Olvera-Bautista, Wall-Medrano, Loarca-Piña, & Campos-Vega, 2021; Froy, 2010). The dietary sources, biological mechanisms, and health benefits of natural chronobiotics are discussed in depth in the following sections.

3.2 Circadian Clock and Diseases

Chronobiology is responsible for the study of circadian rhythms, defined as physical, biochemical, and cognitive changes that follow a 24-hr cycle. The central clock (brain) coordinates the biological clock of each cell causing convenient rhythmicity to sustain homeostatic

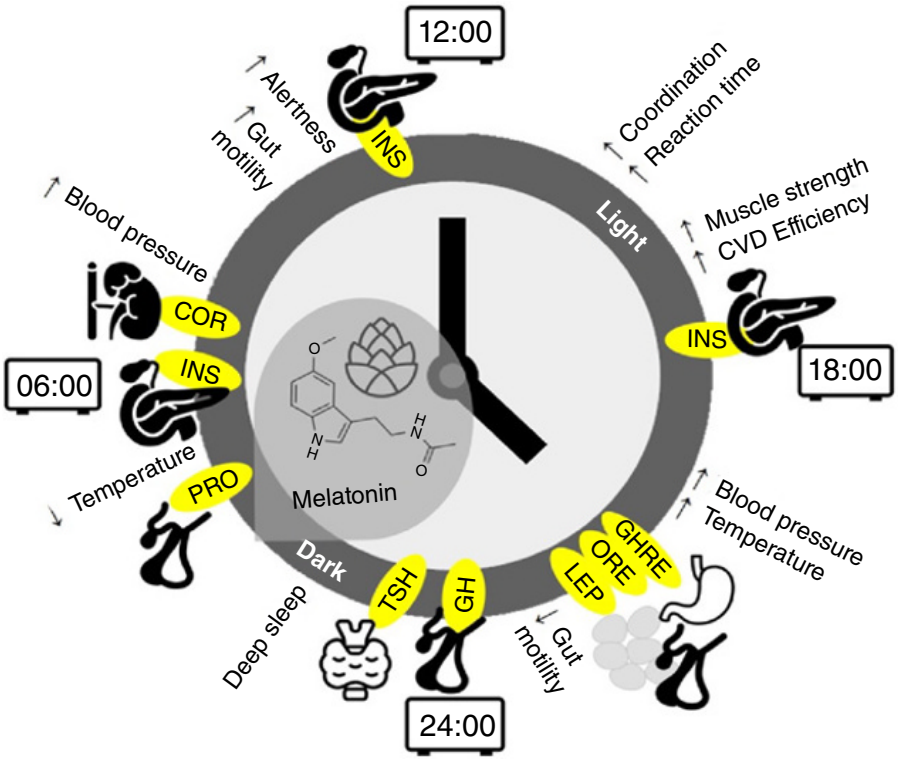

Figure 3.1 Circadian rythm, endocrine response, and body functions are controlled by melatonin. Cortisol (COR), Cardiovascular (CV), ghrelein (GHRE), growth hormone (GH), insulin (INS), leptin (LEP), maximal (↑) and minimal (↓) level, orexins (ORE), metabolite *peak max* (yellow ellypsoid), prolactin (PRO), thyroid-stimulating hormone (TSH). Circadian synthesis of melatonin and peak max ~ 3AM (gray ballon). *Source:* The authors.

processes and survival. Pineal melatonin (N-acetyl-5-hydroxytryptamine) is synthesized from tryptophan in the dark phase of the day and is the main endocrine output signal of the body's timekeeping system (Aulinas, 2020). The rhythmic secretion in mammals is driven by the central (master) circadian clock (oscillator) located in the suprachiasmatic nucleus, a small region in the hypothalamus, situated directly above the optic chiasm (Challet, 2015). Nocturnal secretion of melatonin (peak max at ~ 3 AM; Figure 3.1) is the kick-off signal that delivers the "circadian message" to peripheral circadian clocks during sleep time while decreased daytime melatonin promotes alertness, and this daily melatonin rhythmicity controls the timing of many body functions (Ba-Ali et al., 2019). Binding sites [G protein coupled melatonin receptors (MT_1 and MT_2) and non-receptors (amphipathic sites)] for melatonin have been detected in many areas of the brain (e.g. pars tuberalis and hypothalamus), the immune system, gonads, kidney, liver, and the cardiovascular (CV) system (Aulinas, 2020; Cecon, Liu, & Jockers, 2019).

Peripheral clocks (a.k.a. oscillators) occur in many organs, all synchronized to the master oscillator via direct autonomic and/or endocrine outputs (e.g. leptin, ghrelin, and cortisol; Figure 3.1) and indirect blood-borne metabolites, temporally gated by the CNS (Morris, Aeschbach, & Scheer, 2012; Tsujino & Sakurai, 2012; Challet, 2015; Plano et al., 2017; Chellappa, Vujovic, Williams, & Scheer, 2019). This interconnectivity results in a tightly controlled molecular transcription-translation feedback loops (TTFL) in a 24-hr temporal

framework, and in mammals this TTFL include several genes including CLOCK, *Bmal*1 (aryl hydrocarbon receptor nuclear translocator-like 1; *Arntl/Bmal*1), and clock-controlled genes (*Ccgs*) such as *Periodcircadian protein homologue* 1–3 (*Per*1*, Per*2 and *Per*3) and *Cryptochrome* 1 and 2 (*Cry*1 and *Cry*2) (Beesley et al., 2020; Huang, Lu, & Ho, 2021). Very detailed reviews on the TTFL process and melatonin circadian production have been published (Aulinas, 2019; Crnko, Du Pré, Sluijter, & Van Laake, 2019; Semenova et al., 2021). Any genetic, physiological, or environmental factor leading to chronodisruption and impairment of melatonin synthesis will alter all peripheral clocks, initiating many pathological processes. The intensity of nocturnal light, wakefulness, use of antihypertensives, benzodiazepines, or nonsteroidal anti-inflammatory drugs or alcohol consumption, cause phase-shifting or hypomelatoninemia, while posture at night, exercise, antidepressants, and caffeine increase blood melatonin(Aulinas, 2019). Circadian misalignments further increase the risk for chronic diseases, including obesity (Froy, 2010; Laermans & Depoortere, 2016), cardiovascular disease (CVD) (Chellappa et al., 2019; Crnko et al., 2019), diabetes and insulin resistance (Khandelwal, Dutta, Chittawar, & Kalra, 2017; McMullan, Schernhammer, Rimm, Hu, & Forman, 2013; Stenvers, Scheer, Schrauwen, La Fleur, & Kalsbeek, 2019), osteoporosis (Winter et al., 2021), and cancer (Song et al., 2018), to name a few.

Obesity. The "energetic centers" located in the hypothalamus and brain stem control food intake, sleep/wakefulness, locomotor activity, and energy expenditure (Laermans & Depoortere, 2016). Several cells connected to the network of storage, distribution, and metabolism of energy substrates (e.g. adipose tissue, liver, skeletal muscle, and intestine) have their own circadian machinery (Froy, 2010), and several detailed experiments have revealed the relationship between clock proteins and the expression of enzymes related to basal (during sleep), postprandial (during daylight), and physical activity energy expenditure (Orozco-Solis et al., 2016; Zitting et al., 2018). Clock gene mutant and knockout animals (e.g. ClockΔ19, *Per*1*/Per*2*, Bmal*1*, Cry*1, *and Rev-erbα* mice) often exhibit morbid/early-onset obesity, hyperphagia, hyperleptinemia, hepatic steatosis, and insulin resistance (Laermans & Depoortere, 2016). Conversely, time-imposed physical exercise commonly recommended for obese patients entrains behavioral rhythms (Tahara, Aoyama, & Shibata, 2017), while bariatric surgery modifies the expression patterns of clock proteins in rodents (Kim, Son, Kang, Ha, & Ha, 2015) and night eating syndrome in humans (De Zwaan, Marschollek, & Allison, 2015).

Cardiovascular diseases. Epidemiological observations indicate that individual chronotypes, a measure of preferred timing of sleep and activity, defines its mortality risk from CVD; evening types (e.g. second-shift workers) being at higher risk (Chellappa et al., 2019). Virtually all CV cells (endothelial and vascular smooth muscle cells, myocardial fibroblasts, cardiomyocytes, and cardiac progenitor-like cells) have clock oscillators and the rhythmic expression of clock genes begins during cardiac differentiation. CV cells collectively regulate endothelial function, thrombus formation, blood pressure, and heart rate, while chronodisruption leads to heart failure, cardiomyopathy, myocardial infarction, bradycardia, and TTFL-related proteome/transcriptome abnormalities (Crnko et al., 2019). Nowadays, chronotherapy for CVD considers precise-timing pharmacology to maximize efficacy, novel circadian "omic" chronobiomarkers to define their clinical course, and prognosis and novel pharmacologic compounds (chronobiology drugs) targeting circadian mechanism (Tsimakouridze, Alibhai, & Martino, 2015).

Diabetes and insulin resistance. While the central clock regulates food intake, energy expenditure and systemic insulin sensitivity, peripheral clocks located in enterocytes, hepatocytes, adipocytes, and miocytes regulate the timely absorption, transport, and cellular entry of glucose collectively mediated with the pancreatic oscillator responsible of insulin/glucagon fine-tuning (Stenvers et al., 2019). The strict switching from gluconeogenesis to glycolysis and vice versa, often interrupted in diabetes, is controlled by the hepatic circadian apparatus, while the pancreatic clock is synchronized to the light–dark cycle and the oscillatory expression of its clock genes is glucose-dependent (Qian, Block, Colwell, & Matveyenko, 2013). However, sleep disturbances are very common in diabetic patients (Khandelwal et al., 2017) and functional mutations in the melatonin receptor and lower melatonin secretion linked to insulin resistance (McMullan et al., 2013). Melatonin can be restored by supplementation since it promotes the growth and differentiation of pancreatic cells by stimulating insulin growth factor receptor (IGF-R) and insulin receptor (IR) tyrosine phosphorylation (Sharma, Singh, Ahmad, Mishra, & Tiwari, 2015).

Osteoporosis and cancer. Studies in rodents have demonstrated that bone tissue also has an intrinsic circadian system and disruption of clock genes expression lead to disturbed bone structure and quality. Pronounced rhythms in the bone resorption (e.g. CTX: carboxy-terminal collagen crosslinks) and formation (e.g. osteocalcin) markers and rhythmic production of glucocorticoids indicate that osteoclasts and osteoblasts possess robust diurnal activity patterns in humans with a peak during the rest phase (Winter et al., 2021). Moreover, agonist of the circadian regulators REV-ERBs inhibits osteoclast differentiation, and therefore clock synchronizing therapy may help to correct abnormal bone metabolism (Song et al., 2018). On the other hand, the circadian machinery in many organs modifies the 24-hr rhythmicity of key epigenetic events such as DNA methylation, miRNA expression, and histone modification (Reszka & Zienolddiny, 2018); genetic variation in circadian rhythm and melatonin pathways are common in prostate cancer (Gu et al., 2017) and chemotherapy worsens the rest–activity rhythm and quality of life of breast cancer patients (Sultan, Choudhary, & Parganiha, 2017).

3.3 Regulation of Circadian Clocks

Circadian clocks are internal timing systems that enable organisms to adjust their behavioral and physiological rhythms to their daily environmental changes. These clocks generate self-sustained oscillations at the cellular, tissue, and behavioral level. The rhythm-generating mechanism is based on a gene expression network with delayed negative feedback loop that causes the transcript to oscillate with a period of approximately 24 hr (Srikanta & Cermakian, 2020 and references therein). The circadian clock can be divided into two parts: the master clock, residing in the suprachiasmatic nucleus of the hypothalamus (SCN), and the peripheral clocks that reside in various tissues throughout the body.

Many clock-controlled genes (CCGs) are transcripted by the heterodimerization of two transcription factors: CLOCK, and BMAL1 that binds to E-box sites within their promoters. Those genes generate a tightly self-regulated feedback loop by controlling the transcription of their repressors, period (PER) and cryptochrome (CRY) family members. In response to light, CLOCK interacts with BMAL1 to activate *Per* and *Cry* transcription; the increase in

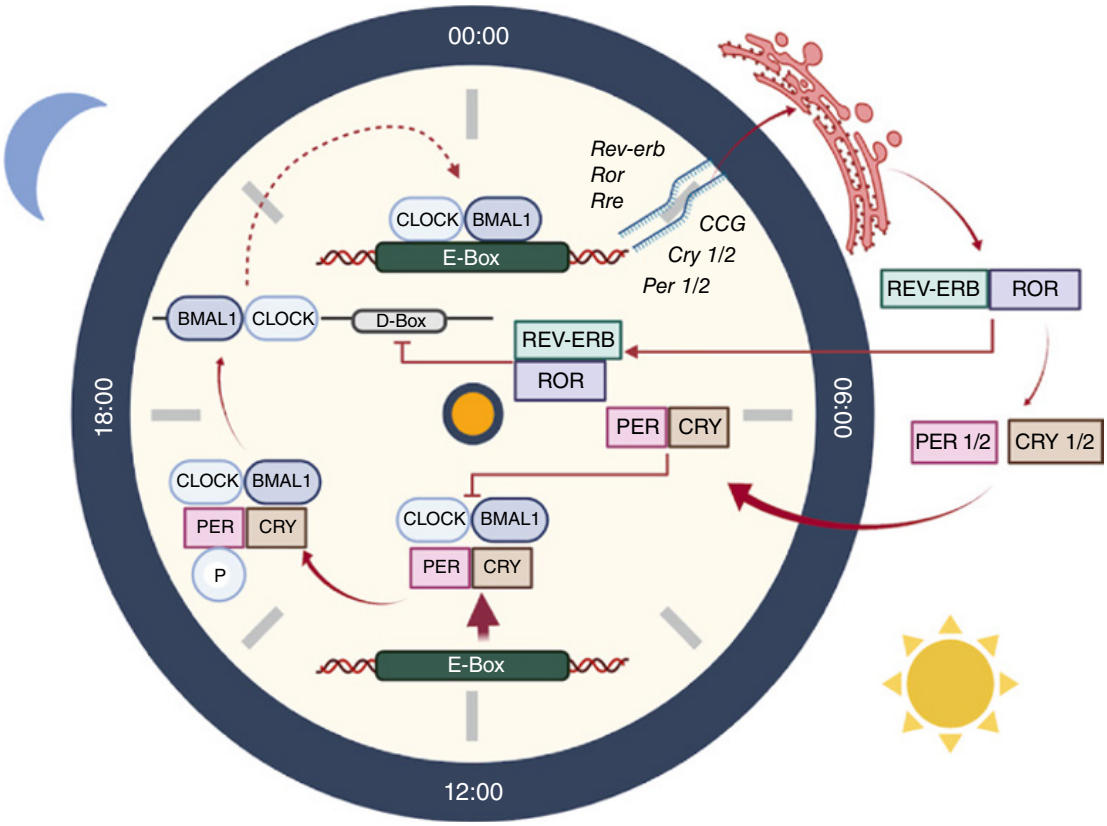

Figure 3.2 The molecular clock. Figure created with BioRender.

these genes transcription results in the accumulation of circadian repressors PER and CRY which heterodimerize, translocate to the nucleus, and inhibit CLOCK/BMAL1-mediated transcription. In response to the decrease/absence of light, the PER/CRY repressor complex degrades, and the cycle begins again. In a secondary feedback cycle, REV-ERB (nuclear receptor) and ROR (retinoic acid receptor-related orphan receptors) participate in regulating BMAL1 expression (Figure 3.2) (Dufoo-Hurtado et al., 2020 and references therein).

The master clock is synchronized or entrained by the light–dark cycle and, in turn, synchronizes clocks present in peripheral tissues and organs. The primary time cue for the molecular clock in the SCN is light detected by the eye. The photoreceptors involved in this process include the rods and cones that mediate vision, as well as the recently identified melanopsin-expressing photosensitive retinal ganglion cells (pRGCs). Light information is conveyed to the SCN via the retinohypothalamic tract, resulting in an intracellular signaling cascade which converges on cAMP response elements in the promoters of several key clock genes (Dannerfjord, Brown, Foster, & Peirson, 2021 and references therein).

Most cells have molecular circadian clocks, and most peripheral tissues are synchronized locally at least at the tissue level showing circadian oscillation of clock genes (peripheral clocks); the phases of peripheral clocks are similar among many tissues. The evidence supports the requirement of the SCN for temporal orchestration of the periphery in living animals. However, a recent study found that even in the absence of SCN or extra-SCN clocks, peripheral clocks remain rhythmic, indicating previously controversial

circadian oscillator coupling within peripheral tissues (Finger & Kramer, 2021). Systemic cues constantly entrain peripheral cell clocks that are easily desynchronized, among them the rhythms of body temperature, the physiological levels of oxygen rhythms, feeding cycles, hormones as well as glucocorticoid and blood concentrations (Oike, 2017 and references therein).

The connections of the mammalian clock system have a conceptual model based on knowledge from the turn of the century, suggesting that the SCN regulates peripheral clocks mainly through feeding-fasting cycles, body temperature cycles, hormones, and blood concentrations. However, a new model of the system has been proposed where in addition to the SCN, other distinct hypothalamic clocks control daily energy homeostasis. The autonomic nervous system (ANS) differentially innervates peripheral tissues and modulates their clocks by adjusting sympathetic tone. All clocks are connected via the circulatory system by an ever-growing list of synchronizing factors, many of which are under local circadian control in peripheral tissues (Koronowski & Sassone-Corsi, 2021 and references therein).

3.3.1 Food as Synchronizer

A general model of circadian entrainment is recognized in which the SCN regulates the phase of peripheral clocks via its control of feeding behavior. Accordingly, the timing of food intake is highlighted as a powerful environmental cue with the potential to destroy or restore the synchrony of circadian rhythms in metabolism (Pickel & Sung, 2020). Restricted feeding has no impact on the central pacemaker in the SCN but alters the secondary oscillators from peripheral tissues such as liver, kidney, heart, and pancreas, indicating that diet regulates peripheral tissue clock oscillators (Dragoi et al., 2019 and references therein). Yamamuro et al. (2020) suggested that constant light exposure induced disruption of both central and peripheral circadian rhythms; time-restricted feeding in mice restored the circadian rhythms of most genes, including *Clock* and *Cry* except *Per*1, to various degrees in both liver and white adipose tissue (WAT), as well as genes involved in lipid metabolism (*Hmgcr, Dgat*1*, Dgat*2*, Atgl, Lipe, Fasn, Lxrα, Pparα, Pparγ, Srebp*1*c, and Srebp*2).

Feeding at the wrong time of the day and diet composition (free choice high-fat-high-sugar diet; fcHFHS) disturb the peripheral clocks in skeletal muscle (SM) and brown adipose tissue (BAT), but to different degrees and thereby result in a further desynchronization between metabolically active tissues such as SM, BAT, WAT, and liver. For example, *Pdk*4 and *Ucp*3 were phase-shifted, while the rhythmic expression was lost for *Ucp*3 in SM on the fcHFHS diet during the light phase (De Goede, Hellings, Coopmans, Ritsema, & Kalsbeek, 2020).

A carbohydrate-containing diet causes strong entrainment through insulin secretion. However, it is unknown whether human diets entrain peripheral circadian clocks. Per gene expression rhythm is altered in monocytes and delays the amplitude of cortisol in humans by changing a higher carbohydrate and lower fat to isoenergetic diet (Pivovarova et al., 2015). The adherence of low carbohydrate diet can improve the circadian rhythm by reducing levels of inflammatory markers in intermediate- and morning-type groups of women (n=304) affected by overweight and obesity, IL-1β and Galectin-3 being the mediating markers (Tavakoli, Mirzababaei, Sajadi, & Mirzaei, 2021). In PER2::LUC knock-in

mice, feeding the control mouse diet (AIN-93M) with a protein: fat: carbohydrate ratio of 14.7 : 9.5 : 75.8 for 2 days during inactive periods, produced significant phase advance (7.3 hr) in the liver clock compared with that in 24-hr fasted mice, whereas human diets caused significant but smaller phase advances (4.7–6.2 hr). Phase advance decreased in adenine-induced chronic kidney disease mice with a normal diet compared with healthy and high-fat/sucrose-induced type 2 diabetes mice. These results support the food-induced entrainment of peripheral clocks in human clinical trials (Yasuda et al., 2019).

The phase *Per*2 mRNA rhythms in WAT was significantly delayed (by 0.97 ± 0.29 hr) with delayed meals (meals at 12:00, 17:00, and 22:00) compared to regular meal pattern (meals at 07:00, 12:00, and 17:00) in 10 healthy young men (Wehrens et al., 2017). However, skipping breakfast for 6 days does not alter clock gene expression in leukocytes albeit the delay (42.0 ± 16.2 min) on the circadian rhythm of the body temperature (Ogata et al., 2020). Breakfast consumption acutely affects clock and CCG expression leading to normal oscillation in healthy individuals and individuals with diabetes (Jakubowicz et al., 2017). Moreover, the level of *Bmal*1, *Rorα*, and *Sirt*1 expression was higher ($P < 0.05$) after lunch on breakfast and lunch day, whereas the other clock genes remained unchanged in healthy individuals. In individuals with type 2 diabetes, *Bmal*1*, Per*1*, Per*2*, Rev-erbα*, and *Ampk* increased ($P < 0.05$) after lunch on the breakfast and lunch day. Interestingly, the omission of breakfast altered clock and metabolic gene expression in both healthy and with type 2 diabetic individuals.

Only a single human study demonstrated that meal timing sufficiently fulfills at least one of the proposed zeitgeber criteria (Aschoff, 1954) according to a recent review (Lewis, Oster, Korf, Foster, & Erren, 2020). The review also suggests preference for nonparametric analyses instead of modeling, and that such studies should be undertaken under real-life conditions aiming to devise practical recommendations for chronodisruptive work or environmental conditions.

Recent studies also suggest that natural food intake has little or null synchronizing effect on peripheral circadian clocks. Xie et al. (2020a) evaluated the effects of normal feeding patterns on phase shift or entrain peripheral tissues by measuring circadian rhythms of the liver, kidney, and submandibular gland in $mPer2^{Luc}$ mice under different food schedules. In experiment 1, a 12-hr shift of the simulated natural food provision schedule resulted in small shifts in the liver and kidney and no shift in the submandibular gland. In experiment 2, the light–dark cycle was removed to determine entrain peripheral clocks on continued scheduled food. Peripheral organ phase was nevertheless best predicted by the rest–activity cycle; food significantly entrained only one of 12 kidneys and one of 12 livers. As a positive control, time-restricted feeding was an effective zeitgeber in both experiments, unlike the simulated natural feeding. Thus, they infer that under normal conditions of food intake, the SCN remains the dominant synchronizer of peripheral clocks without requiring the intermediate step of feeding behavior. The same group (Xie et al., 2020b) evaluated the efficacy of naturalistic feeding patterns on phase shift and peripheral tissues entrainment, measuring circadian rhythms of the liver, kidney, and submandibular gland in $mPer2^{Luc}$mice under different feeding schedules. In *ad lib* feeding, as well as in a schedule designed to mimic the *ad lib* pattern, PER2::LUC bioluminescence peaked during the night as expected. Surprisingly, shifting the scheduled feeding by 12 hr caused only small advances (< 3 hr). To isolate the effects of feeding from the light–dark cycle, clock phase was then measured

in mice acclimated to scheduled feeding and housed in constant darkness. In these conditions, peripheral clock phases were better predicted by the rest–activity cycle than the food schedule. Under natural feeding patterns, the master pacemaker in the brain sets the phase of peripheral organs independent of feeding behavior.

3.4 Chronobiotics as Functional Foods

Circadian rhythm disorders negatively influence health and have no current medical treatment. However, chrononutrition is becoming a tool to enhance nutritional health-related status; particularly, some natural compounds have proved their potential to synchronize and restore the clocks, identified as chronobiotics (Dufoo-Hurtado et al., 2020 and references therein). Chronobiotics are defined as drugs able to synchronize or increase the amplitude of the circadian rhythms. Melatonin, produced mainly by the pineal gland, an unusual phylogenetically conserved compound present in all known aerobic phyla is the most relevant prototype (Cardinali, 2019 and references therein).

Dietary compounds entrain the circadian rhythm in many peripheral tissues. For example, the consumption of nobiletin, L-theanine, L-ornithine, and resveratrol can benefit people in maintaining proper circadian rhythms and keeping good health condition; however, the mechanism is still unknown (Cheng et al., 2021 and references therein). CLOCK, BMAL1, and PER respond to metabolites and xenobiotics due to their Per-Arnt-Sim (PAS) domains containing structures, and hormonal ligands and metabolites such as sterols can activate the nuclear receptors REV-ERB and ROR (Koronowski & Sassone-Corsi, 2021 and references therein).

A comparative circadian metabolomic analysis on serum and liver in mice under high-fat diet revealed that the nutritional challenge reduces serum metabolite rhythmicity compared with liver, indicating a circadian misalignment between the analyzed tissues (Abbondante, Eckel-Mahan, Ceglia, Baldi, & Sassone-Corsi, 2016). A high-fat diet, which induces the disruption of the normal circadian cycle enables large-scale genesis of de novo oscillating transcripts, resulting in reorganization of the coordinated oscillations between coherent transcripts and metabolites. This reprogramming involves both the impairment of CLOCK: BMAL1 chromatin recruitment and a pronounced cyclic activation of surrogate pathways through the transcriptional regulator PPARγ (Eckel-Mahan et al., 2013).

3.4.1 Nutrients

Several circadian clock proteins as well as their accessory proteins (such as nuclear receptors) are highly sensitive to nutrient metabolism. Macro and micronutrients can function as zeitgebers for the clock in a tissue-specific way and can thus impair synchrony between clocks across the body, or potentially restore synchrony in circadian misalignment. Circadian nuclear receptors are particularly sensitive to nutrient metabolism and can alter tissue-specific rhythms in response to changes in the diet. The SNPs in human clock genes is apparently correlated with diet-specific responses and along with chronotype eventually may provide valuable information from a clinical perspective using diet and nutrition to treat metabolic disorders (Ribas-Latre & Eckel-Mahan, 2016 and references therein).

Many circulating nutrients and hormones, such as glucose, amino acids, insulin, glucagon, glucocorticoids, and others, possess zeitgeber capacity (Reinke & Asher, 2019 and references therein).

Timing is important for nutrition along with quality and quantity. Dietary components, such as fiber, unsaturated fatty acids, and polyphenols, at suitable times can promote health (Oike, Oishi, & Kobori, 2014). Interestingly, the daily access to a palatable meal can entrain the SCN; several stimuli can be implicated in this process including motivation and arousal (Mendoza, Angeles-Castellanos, & Escobar, 2005). In the SCN, *c-Fos* expression peaked at palatable meal time and PER-1 showed a peak during the onset of subjective night, as predicted according to the behavioral entrained pattern. In Wistar rats, a daily piece of chocolate coupled to the onset of the active phase (breakfast) accelerated re-entrainment in a jet lag model by setting the activity of the SCN to the new cycle. Furthermore, in a rat model of shift work, a piece of chocolate for breakfast prevented circadian desynchrony by increasing the amplitude of the day–night *c-Fos* activation in the SCN. Contrastingly, chocolate for dinner prevented re-entrainment in the jet lag condition and favored circadian desynchrony in the shift work models. Moreover, chocolate for breakfast resulted in low body weight gain, while chocolate for dinner increased body weight (Escobar et al., 2020).

3.4.1.1 Glucose

Carbohydrates, including glucose, have been proposed as zeitgeber in humans for the food-entrainable peripheral oscillators. The SCN is the principal driver of circadian blood glucose fluctuations by scheduling food ingestion to the activity phases. Low glucose levels during fasting in the rest phase are replenished via circadian glucose excretion from the liver, which is mediated by clock dependent expression of GLUT2, which peaks during the rest (fasting) phase (Gachon, Loizides-Mangold, Petrenko, & Dibner, 2017 and references therein). Two of the most abundant circulating nutrients for cellular energy generation besides glucose, namely, glutamine and lactate, have been linked to feedback signaling pathways for circadian clock control. Glucose and glutamine are converted through the hexosamine pathway into uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc), the substrate for the covalent modification of proteins by *O*–β-d-*N*-acetylglucosamine (*O*-GlcNAc). *O*-glcNAcylation of BMAL1, CLOCK, and PER2 regulates their transcriptional activity and stability affecting entrainment and period length of the circadian clock (Reinke & Asher, 2019 and references therein).

Evening carbohydrate-rich meal, approximately 8 hr after the consumption, increases the core body temperature. While, morning carbohydrate-rich meals significantly advance circadian phase position in the same parameter ($+59 \pm 12$ min) and heart rate ($+43 \pm 18$ min) compared to evening carbohydrate-rich meals (Kräuchi, Cajochen, Werth, & Wirz-Justice, 2002). Hirao, Tahara, Kimura, and Shibata (2009) showed that balanced diets containing carbohydrates/sugars and proteins are good for restricted feeding-induced entrainment of the peripheral circadian clock, and that a balanced diet that increases blood glucose, but not by sugar alone, is suitable for entertainment. However, early investigation suggested that glucose induced clock resetting by downregulating *Per*1 and *Per*2 in Rat-1 fibroblasts (Hirota et al., 2002), while other group showed that glucose has zeitgeber properties for the feeding entrainable oscillator in rats (Stephan & Davidson, 1998). The circadian behavior and peripheral circadian clocks in mice are altered when animals are fed

during 2 weeks with a low-carbohydrate, high-protein diet. This diet induced hypoglycemia without affecting body weight, although the mice consumed more calories. Furthermore, the circadian mRNA expression of clock genes, such as *BMAL*1, *Cry*1, *NPAS*2, and *Rev-erbα*, was significantly phase-advanced, and mean expression levels of *BMAL*1 and *Cry*1mRNAs were significantly elevated in the liver and kidneys of the animals (Oishi, Uchida, & Itoh, 2012).

Rapidly digested starch is appropriate for peripheral clock entrainment. An α-potato starch-substituted diet in PER2::LUCIFERASE knock-in mice induced larger phase delays of the liver clock than did β-potato starch. *Per*2 and *Ror-γ* expression increased in response to α-potato starch administration (Itokawa et al., 2013).

3.4.1.2 Amino Acids

Some of the first studies in the sixties reported the daily rhythms of amino acids concentrations in human plasma (Feigin, Klainer, & Beisel, 1967; Rapoport, Feigin, Bruton, & Beisel, 1966; Wurtman, Rose, Chou, & Larin, 1968). Krüppel-like factor 15 (KLF15) is a critical mediator of branched-chain amino acids (BCAAs) leucine, isoleucine, and valine catabolism and rhythmicity, influencing processes ranging from gluconeogenesis during fasting to nitrogen homeostasis (Fan, Hsieh, Sweet, & Jain, 2018 and references therein). The promoter region of KLF15 has four E-box binding sites for the core clock genes CLOCK and BMAL1, which are positive KLF15 regulators. Therefore, KLF15 is crucial for imparting diurnal rhythmicity to the release, uptake, and utilization of several substrates, notably BCAAs.

This has been supported by the lack of a direct relation between dietary protein and blood amino acid values; for example, normal periodicity or amino acids are maintained in adults despite long starvation periods or complete restriction of dietary protein intake (Feigin, Beisel, & Wannemacher Jr, 1971 and references therein). Also, amino acids availability is reduced by high-protein diets (Moundras, Remesy, & Demigne, 1993). However, amino acids rhythmicity is altered by the onset of an acute illness, including obesity. Valine, leucine, isoleucine, tyrosine, and phenylalanine increased and glycine decreased in obese subjects compared with age- and sex-matched normal-weight subjects, phenomena linked to insulin ineffectiveness (Felig, Marliss, & Cahill Jr, 1969).

Similar results have recently been published. Diets of 100% glucose, 100% casein, 100% starch, and 100% soybean oil fail to significantly advance phase in *Per*2::luciferase knock-in mice. However, 86% glucose with 14% casein significantly advance phase compared to 100% sucrose alone. Nevertheless, a balanced diet properly entertains signals of the mouse liver clock. Nutrients containing glucose and amino acids rapidly change the expression of clock genes, especially *Per*2 and *Rev-erbα*, resulting in a phase shift in mice (Tahara, Otsuka, Fuse, Hirao, & Shibata, 2011).

Conversely, tryptophan and some products modulate light-dependent regulation of circadian rhythm by triggering aryl hydrocarbon receptor (AhR). Both tryptophan and its product 6-formylindolo (3,2-b) carbazole (FICZ) increase cytochrome P4501A1 (*CYP1A*1) and alter the circadian expression of *Per*1, *Cry*1, and *Cry*2 genes in SCN 2.2 cells (Mukai & Tischkau, 2007). Methionine feeding significantly influences the fluctuation of relative mRNA expression of *Clock, Bmal*1*, Cry*1*, Cry*2*, Per*2, and *Per*3 during a day, affecting the rhythmic fluctuation of amino acid transporter in hen's jejunum (Yi-lin et al., 2018).

Elevated supply of methionine and arginine influences α-s1-casein protein synthesis of primary bovine mammary epithelial cells through changes in the mTORC1, circadian clock (*Per*1 *and Clock*), and AMPK pathways (Hu et al., 2020). Yamaguchi (2018) proposes that the neuronal circuit mediated by arginine vasopressin (AVP)/V1 receptor signaling in the SCN plays a crucial role in the resilience of the circadian clock to jet lag. Spengler, Kuropatwinski, Schumer, and Antoch (2009) identified a conserved cluster of serine that include Ser431 which is a prerequisite phosphorylation site for generating BMAL-dependent phospho-primed CLOCK and for the potential GSK-3 phosphorylation at Ser427. Serine loop underlies differential affinity of cryptochromes for *Clock: Bmal*1 to control circadian timing (Fribourgh et al., 2020).

3.4.1.3 Dietary Fiber

Microbiota-derived SCFAs and organic acids produced by the fermentation of nondigestible fiber can communicate from the microbiome to host tissues and modulate homeostasis in mammals. The microbiome has circadian rhythmicity and helps the host circadian clock function (Tahara et al., 2018). Due to this, dietary fibers and prebiotics have been proposed as novel dietary approach to attenuate circadian misalignment, modulating the expression and phase of circadian clock genes.

Tahara et al. (2018) provided the first evidence that high-fiber diets (cellulose) enhanced refeeding-induced peripheral clock entrainment. They found that microbiota-derived SCFA or lactate modulates the phase of host peripheral clocks *in vivo*. Thereafter, our research group demonstrated that antioxidant dietary fiber isolated from spent coffee grounds improved chronotype and circadian locomotor activity in young adults (Oseguera-Castro et al., 2019). In C57BL/6J mice subjected to weekly shifted light–dark cycle under a high-fat diet, beta-glucan (0.2 g day^{-1}) and insulin (0.2 g day^{-1}) reverses the phase delay of *Period* 1 and *Period* 3 in the hypothalamus and reverses the phase delay of *Period* 2 in the liver (Cheng, Lam, Kong, & Cheung, 2020). The observed effects may be due to small chemical compounds exclusively produced by the gut microbiota from undigested carbohydrates. Among them, 3-(4-hydroxyphenyl) propionic acid (4-OH-PPA) and 3-phenylpropionic acid (PPA), the major metabolites exclusively produced by *Clostridium sporogenes*, increase the amplitude of both PER2 and *Bmal*1 oscillation of peripheral and central clock machineries of mice, in a dose-dependent manner following their administration immediately after the nadir or the peak of their rhythm (Ku et al., 2020).

Butyrate, one of the SCFAs produced from dietary fiber by gut microbiota, regulates B cell genes in human submandibular gland cells by increasing IL-10-producing B (B10) cells and decreasing IL-17-producing B cells, through the circadian clock genes RAR-related orphan receptor alpha and nuclear receptor subfamily 1 group D member 1. This acid may ameliorate Sjögren's syndrome, an autoimmune disease caused by inflammation of the exocrine gland (Woo et al., 2021).

The direct addition of butyrate to an *in vitro* hepatic model significantly affects clock component expression. Butyrate heightened the amplitude and shifted the phase of the expression of clock components *Bmal*1 and *Per*2, suggesting that bacterial metabolites can potentiate clock oscillations (Leone et al., 2015). Conversely, the circadian clock regulates the diurnal levels of microbial SCFAs and their rhythmic effects on colon contractility in mice. Diurnal microbial SCFA levels regulate the rhythm of the SCFA receptor *Ffar*3

expression in the colonic myenteric plexus, which causes rhythmicity in SCFA-induced colonic motility. The deletion of *Bmal*1 abolishes rhythmicity of SCFA levels and their downstream effects (Segers et al., 2019).

3.4.2 Phenolic Compounds

Phenolic compounds are secondary metabolites widely distributed in plants. They are synthesized by different pathways such as pentose phosphate, shikimate, and phenylpropanoid; they are classified according to their chemical structure and biosynthesis route (Vuolo, Lima, & Junior, 2019). Phenolic acids, flavonoids, and tannins are the major phenolic compound classes found in foods and are associated with beneficial effects on obesity, diabetes, cancer, and CVDs (Heleno, Martins, Queiroz, & Ferreira, 2015). Furthermore, the potential of phenolic compounds on the adjustment of circadian clocks in peripheral tissues has recently been evaluated.

3.4.2.1 Phenolic Acids

Phenolic acids are a group of phenolic compounds that contain carboxylic acid and are present in various foods. They are commonly linked to amides, esters, or glycosides and are very rarely found free. In its classification, two subgroups are distinguished: hydroxybenzoic acids and hydroxycinnamic acids, and the most representative of both groups are ferulic, coumaric, gallic, vanillic, and protocatechuic acids, among others. This group is characteristic for its small size, high *in vitro* antioxidant capacity, its effects as an antidiabetic and antimicrobial agent, and cancer treatment (Kumar & Goel, 2019). However, its effect on circadian clocks has recently been studied.

Cinnamic acids and their derivatives are bioactive compounds of natural origin present in plants. They are synthesized from precursors such as phenylalanine and tyrosine via the shikimic acid route. The best known and most abundant are cinnamic, ferulic, and caffeic acids and their derivatives. These compounds have received great attention recently due to their numerous health benefits, including neuroprotective, analgesic, anti-inflammatory, antioxidant, and antidepressant effects, among others (Adisakwattana, 2017). The administration of this group of compounds evaluated recently *in vivo* models showed that cinnamic acid shortens the circadian period of circadian rhythms directly and indirectly through the central clock in the SCN, and the locomotor rhythm in animals. All the above suggests that dietary intake of cinnamic acids and their derivatives can help prevent and treat circadian disorders. However, so far, the molecular mechanisms through which the effect is expressed have not been explored (Oishi, Yamamoto, Oike, Ohkura, & Taniguchi, 2017).

Chicoric acid is a hydroxycinnamic acid, an ester of caffeic acid, a member of the phenylpropanoid family. It is found mainly in the roots of plants such as chicory, purple coneflower, and basil; it is primarily associated with antiviral, anti-inflammatory, glucose, and lipid homeostasis effects (Peng, Sun, & Park, 2019). Its regulatory effects on lipid metabolism have recently been associated with the circadian clock. Chicoric acid improves the morphology and levels of hepatic lipids in a dose-dependent manner. Also, this phenolic acid regulates the expression of the circadian clock genes and their daily oscillations. The beneficial effects of this acid in the regulation of lipid metabolism were associated with the

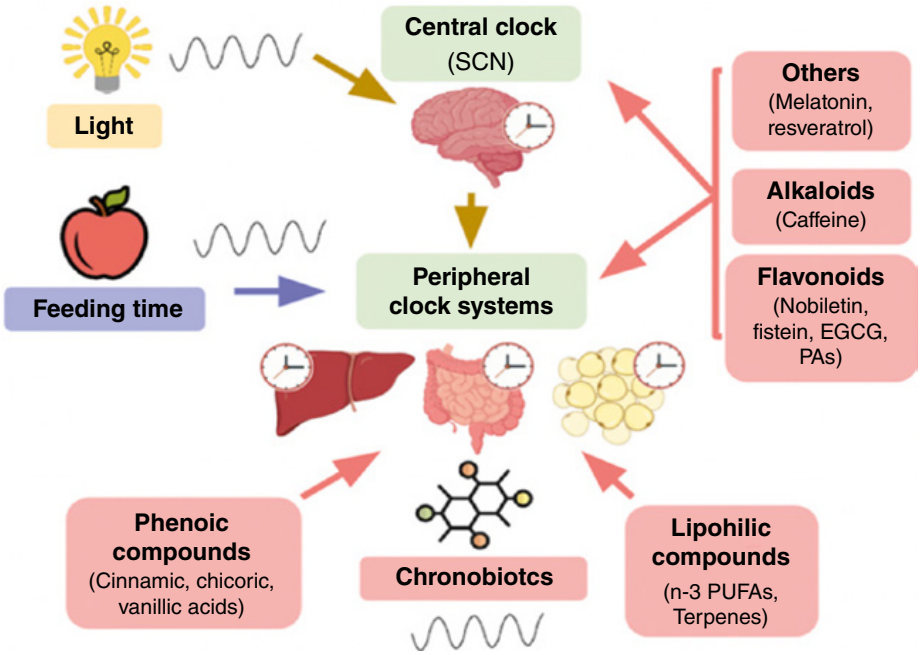

Figure 3.3 Food bioactive compounds with chronobiotic potential. *Source:* The authors.

regulation of circadian clocks through BMAL-1, a key component of the circadian clock that plays an essential role in adipocyte maturation and differentiation. It is suggested that the mechanism may involve BMAL1 regulating the expression of essential components of lipid synthesis and degradation such as fatty acid synthase (FAS), acetyl CoA carboxylase (ACC), peroxisome proliferator-activated receptor α (PPARα), and liver X receptor α (Lxrα) through the Akt/GSK3β signaling pathway in a BMAL-1-dependent manner (Guo et al., 2018; Figure 3.3). Therefore, chicoric acid is a promising chronobiotic that modulates circadian rhythms to improve metabolic syndrome, nonalcoholic fatty liver disease, among other conditions.

Vanillic acid is a hydroxybenzoic acid with several potential health benefits, including its antioxidant capacity and anticancer properties. The administration of vanillic acid in rats with induced endometrial carcinoma slows the development of tumors, improves the amplitude, and reverses the phase delay of the circadian rhythm of enzymes of the antioxidant system such as superoxide dismutase (SOD) (Bhavani, Subramanian, & Shanmugapriya, 2016; Figure 3.3).

3.4.2.2 Flavonoids

Flavonoids constitute the group of phenolic compounds with the greatest distribution in plants. They are characterized by their low molecular weight and their structure consisting of two aromatic rings joined by a three-carbon bridge, often in the form of a heterocyclic ring. Variations in substitution patterns result in various flavonoid subgroups such as flavonols, flavones, flavanones, flavanols (catechins), isoflavones, flavanonols, and anthocyanidins (Vuolo et al., 2019). Flavonoids have been reported to affect the circadian rhythm. This group of compounds includes nobiletin, fisetin, myricetin, and hesperidin, which mainly affect the amplitude of the circadian rhythm (Figure 3.4). Fisetin is a flavonoid

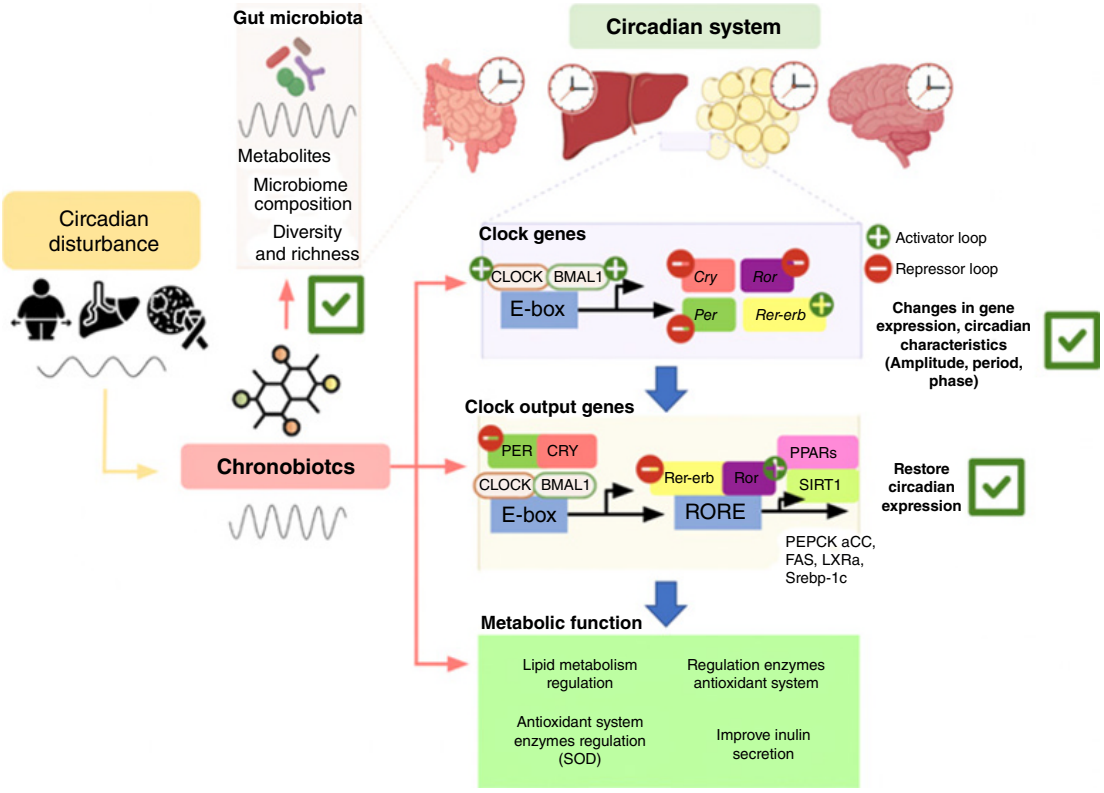

Figure 3.4 Food bioactive compounds with chronobiotic potential: molecular mechanisms and metabolic effects. *Source:* The authors.

distributed mainly in fruits. The effect of fisetin consumption evaluated in an *in vivo* model reduced fragmentation and restoration of the circadian pattern of rest–activity in animals with hyperammonemia (Subramanian et al., 2015). However, there are no molecular studies of the mechanism through which this is carried out.

Nobiletin is a polymethoxy flavonoid widely distributed in the peel of citrus fruits and the pulp of fruits. It is recognized for its effects in attenuating inflammatory, metabolic, Alzheimer's processes, among others. Its effects have also been evaluated on circadian rhythms. In the first investigation with an *in vivo* model of diet-induced obesity, nobiletin improved circadian rhythms in the liver through the activation of the orphan receptor tyrosine kinase (ROR), increasing circadian genes expression, resulting in the prevention of metabolic syndrome in a circadian clock-dependent manner (He et al., 2016). One year later, Shinozaki et al. (2017) evaluated *in vitro* the chronic or transient exposure of 18 different flavonoids (flavones, flavonols, isoflavones, catechins, and polymethoxy flavonoids) on the amplitude, period, and phase of *Per*2. The results showed that although the compounds share a large part of the chemical structure, *Per*2 expression varied, even when the compounds were from the same subfamily. However, it is emphasized that only polymethoxy flavones such as tangeretin and nobiletin improve amplitude, period, and phase delay.

Epigallocatechin gallate (EGCG), better known as epigallocatechin-3-gallate, is the most abundant bioactive compound in various teas, including green, black, and white, in fruits, nuts, among others. Structurally, this molecule is an ester of epigallocatechin and gallic

acid and has been studied for its beneficial effects, including its antioxidant, anti-inflammatory, and antiproliferative capacity, among others (Aggarwal et al., 2020). Besides, there has been particular interest in the research of this compound as a regulator of the circadian system. EGCG modifies clock gene oscillations (*Clock* and *Bmal*1) in the hypothalamus, liver, and adipose tissue in *in vivo* studies. It also reduces circadian desynchronization and energy imbalance in BAT, the metabolism controlled by the clock maintains lipid homeostasis in WAT, and improves insulin sensitivity in an animal model of circadian misalignment caused by a Western diet. These processes occur through changes in genes expression of the clock system such as *Clock, Bmal*1 and *Cry*1*, Sirt*1 and PGC1α, which in turn modify the expression of lipid metabolism genes such as *PPARγ,* and negatively regulate lipids accumulation (Li, Kek, Lim, Gelling, & Han, 2016; Mi et al., 2017; Figure 3.3). *In vivo* and *in vitro* models of neuroblastoma cells and mouse primary hepatocytes exposure to EGCG modifies the expression of circadian clock genes and prevents oxidative stress and mitochondrial dysfunction in a BMAL1-dependent manner (Qi et al., 2017; Qi et al., 2018). In an *in vivo* model of constant darkness, insulin resistance and glucose and lipid metabolism improve in the liver, suggesting that green tea polyphenols such as EGCG can also synchronize the center clock in the suprachiasmatic nucleus and positively affect cognitive impairment (Qi et al., 2017). Previous evidence suggests the potential for this chronobiotic to maintain the relationship between the circadian clock and oxidative stress and thus mitigate age-related neurodegenerative and metabolic diseases.

EGCG also has proven beneficial effects in different eye diseases. Retinitis pigmentosa (RP) is a disease that involves visual function and patients with this condition present dysfunction of circadian rhythmicity. Furthermore, the retina plays an essential role in synchronizing the circadian clocks. RP exhibits characteristic age-related degenerative effects on the melanopsin system and is associated with weaker circadian patterns (Lax et al., 2016). The effect of EGCG consumption was evaluated on the loss of photoreceptors and its association on biological rhythms of circadian clock output (temperature and circadian activity). However, the results did not show a clear relationship with the effect of EGCG on circadian rhythmicity in the evaluated output variables, and more studies are necessary (Perdices, Fuentes-Broto, Segura, Cuenca, & Pinilla, 2020).

The gut microbiome is of vital importance in maintaining the host's circadian rhythm and affecting its health. Most bacterial communities of the microbiota have circadian characteristics, which help maintain homeostasis through metabolic processes. As mentioned above, catechins can modify the rhythmicity of the circadian clocks of peripheral organs (Leone et al., 2015). Furthermore, EGCG and derivatives of these compounds such as epicatechin gallate (ECG), epigallocatechin (EGC), and epicatechin, and methylated forms of EGCG exert prebiotic potential (Zhang et al., 2013). An emerging area is the study of chronobiotics on the intestinal microbiota and their relationship with the circadian rhythm. The modification of the intestinal microbiota is believed to be the molecular mechanism of action of this chronobiotic. Oolong tea is a fermented beverage that contains numerous catechins such as EGCG. Guo et al. (2019) evaluating oolong tea on the intestinal microbiota in an *in vivo* model with the circadian disorder showed improved richness and diversity of the colonic microbiota after treatment. The molecular mechanism through which this beneficial effect occurs includes interactions with the development of beneficial bacteria and producers of SCFAs, metabolic aspects of the bacteria,

and interference with the function of the cell membrane and bacterial energy metabolism. All the above suggest the chronobiotic potential of catechins such as EGCG to reduce conditions such as metabolic syndrome associated with circadian disorders. Zhang, Yan, and Wu (2020) recently evaluated the main catechins in green tea on the intestinal microbiota composition. Their results agree with previous report (Guo et al., 2019). In addition, an analysis of the associated metabolic pathways suggests that the molecular mechanism that may be involved in modifying the microbiota includes the activation of genes relevant to ubiquinone, another biosynthesis of terpenoids-quinones, pentose, and tautomeric glucuronate, and the biosynthesis of lipopolysaccharides which were found to be differentially expressed.

Proanthocyanidins (PAs) are polymers of flavonoids known as condensed tannins. These compounds are found abundantly in flowers, nuts, fruits, and seeds. They are formed by catechin and epicatechin units. They are recognized for their impact on astringency and their biological potential as antioxidant, neuroprotective, cardioprotective, antidiabetic agent, among others (Rauf et al., 2019). However, their effect as a chronobiotic has also been evaluated.

Grape seeds are a good source of PA. The effect of extracts from this natural source on the expression of the circadian clock system genes has been evaluated *in vivo* and *in vitro* models of different peripheral tissues. An acute dose of PA acts as a synchronizer to maintain nocturnal melatonin levels in the first 3 hr of the light phase. Also, PA administration modulates the molecular clock in the liver. This effect may occur due to regulation in the expression of BMAL1, RORα, *Nampt*, and NAD, which suggests the transactivation of RORα, overexpressing BMAL1. Its administration also affects the expression of genes of the central clock system of the hypothalamus (Ribas-Latre, Baselga-Escudero et al., 2015; Ribas-Latre, Del Bas, Baselga-Escudero, Casanova, Arola-Arnal, Salvadó, Bladé et al., 2015; Ribas-Latre, Ribas-Latre, Del Bas, Baselga-Escudero, Casanova, Arola-Arnal, Salvadó, Arola et al., 2015; Figure 3.3).

3.4.2.3 Others

Resveratrol is a stilbenoid polyphenol with several recognized therapeutic effects. A good source of this compound is grapes and wine (Singh et al., 2019). It has been associated with the prevention and progression of various diseases through various mechanisms, including a chronobiotic mechanism (Figure 3.4). Its chronobiotic potential has been evaluated *in vivo* with mice fed a high-fat diet. The results demonstrate that resveratrol intake affects the circadian expression of *Sirt*1 and *Rev-Erbα* in the liver to restore clock genes and the circadian expression of PPARα, which in turn regulates the expression of genes related to lipid metabolism like Srebp-1c, Fas, and Acc1 (Sun et al., 2015, Figure 3.3).

3.4.3 Lipophilic Compounds

Hydrophobicity is the main characteristic of lipophilic compounds. These compounds exert positive effects on different physiological, nutritional, and structural processes in the human body. Examples of these compounds are polyunsaturated lipids, oil-soluble vitamins, phytosterols, curcuminoids, carotenoids, terpenes, among others (Raikos & Ranawana, 2017).

3.4.3.1 Unsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) contain two or more double bonds and are classified as *n*–3 or *n*–6, according to the position of the last double bond in the carbon chain concerning the terminal methyl end of the molecule. The main dietary sources of these compounds are vegetable oils (*n*–3) and foods of animal origin such as fish, salmon, tuna, and trout (*n*–6). The three main n-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Schmitz & Ecker, 2008). The importance of adequate consumption of PUFA *n*–3 derived from fatty marine fish, specifically EPA and DHA, in development, CV health, and maintaining health has been highlighted (Calder, 2015). Furthermore, the investigation of the effect of PUFAs as chronobiotic potentials has also had a significant impact (Figure 3.4). In an *in vivo* model, fish oil EPA/DHA consumption significantly induced phase changes in the expression of circadian clock genes (*Per*2) in the liver. It has a positive physiological effect through increase in insulin secretion due to GPR120 (a polyunsaturated fatty acids receptor) interaction (Furutani et al., 2015; Figure 3.3). Recently, Serhiyenko, Segin, and Serhiyenko (2018) evaluated the effect of *n*–3 PUFA consumption on circadian rhythmicity measured through heart rate variability in patients with diabetes mellitus 2 and autonomic CV neuropathy in a clinical study. Patients consuming one capsule mainly containing EPA/DHA per day for 3 months showed positive changes in parameters of heart rate variability during periods of activity and rest.

Finally, the effect of *n*–3 PUFAs in fish and algae oils has been evaluated *in vivo* in improving hyperlipidemia by modifying the circadian rhythm of the intestinal microbiota; changes of bacteria were significantly different between ZT0 (active period) and ZT12 (resting period). The gut microbiota in mice fed high-fat and fructose diets can be improved by supplementing *n*–3 PUFAs-rich oils by restoring the circadian rhythms of the microbiota, modulating some intestinal bacteria associated with the metabolism of serum lipids, and the production of SCFAs (Gui et al., 2019).

3.4.3.2 Terpenoids

Terpenes are organic compounds that are characterized by giving plants smell and color. They consist of isoprene units and are named for every five carbon atoms as hemiterpenes (C5), monoterpenes (C10), diterpenes (C20), and triterpenes (C30) (Mukherjee, 2019). This last group of compounds has been widely evaluated for its pharmacological activities, including anti-inflammatory, antidiabetic, anticancer, and antioxidant activities. Some triterpenes include corosolic acid, celastrol, and cucurbitacins present in Banaba tea leaves (*Lagerstroemia speciosa* L.), *Tripterygium wilfordii*, and cucurbits such as pumpkin, cucumber, melon, among others. The chronobiotic potential of these compounds has recently been evaluated in an *in vitro* model. Suzuki, Fukumitsu, and Oike (2021) evaluating the effect of 15 commercial triterpenes, including analogs of 3 main groups: corosolic acid, celastrol, and cucurbitacins, in osteosarcoma and fibroblast cell lines on PER2 expression showed a dose-dependent effect for each group of compounds with only some of the compounds modifying the circadian clock presumably due to the structure of each compound.

Corosolic acid, celastrol, and cucurbitacin B can reset and synchronize the circadian clock by increasing the expression of clock genes such as *Per*2 (Figure 3.3). In particular, celastrol shortens the period length in fibroblasts. This result illustrates the potential of this

group of compounds as future chronobiotic ingredients that can prevent various diseases through circadian clocks adjustment (Figure 3.4).

3.4.4 Alkaloids

Alkaloids are an important group of secondary metabolites widely distributed in nature. Their structure contains one or more nitrogen atoms, particularly as part of a heterocyclic ring, and most have toxic effects on organisms. Among the most important are caffeine, capsaicin, piperine, theobromine, theophylline, among others. They are characteristic for their effects as activators or depressants of the central nervous system (Debnath et al., 2018).

3.4.4.1 Caffeine

Caffeine is the most consumed stimulator of the nervous system, which works by blocking adenosine binding to its receptor. Dietary sources of caffeine include coffee, tea, yerba mate, caffeinated soft drinks (cola-type), and energy drinks (Reyes & Cornelis, 2018); which are consumed to relieve drowsiness for a long time, which is why its effect as a chronobiotic has also been of particular interest. *In vivo*, *in vitro*, and *ex vivo* models indicate that this psychostimulant affects the circadian rhythm by lengthening the circadian period in mouse liver explants. Simultaneously, in the suprachiasmatic nucleus, it delays circadian rhythm and lengthens the circadian locomotor rhythm of animals (Oike, Kobori, Suzuki, & Ishida, 2011; Figure 3.4). Human studies suggest that caffeine also influences circadian physiology increasing daytime exposure to sunlight and reducing light at night. Consuming caffeine causes a phase delay; nonetheless, this depends on its consumption time. Its chronobiotic effects are explained by affecting the cyclic adenosine monophosphate (cAMP)-dependent receptor, suggesting that caffeine modifies the circadian rhythm through a blockade of this receptor (Burke et al., 2015). Caffeine also improves alertness without affecting circadian clock synchronization and light responsiveness at the level of the suprachiasmatic nucleus (Hilaire & Lockley, 2015; McHill, Smith, & Wright Jr, 2014; Van Diepen et al., 2014).

3.4.5 Others

3.4.5.1 Melatonin

Melatonin is a ubiquitous hormone found in various organisms. According to its chemical structure, it belongs to the family of indoleamine. In humans, this hormone is produced mainly in the pineal gland and is closely associated with regulating the circadian clock and peripheral oscillators, allowing the temporary organization of biological functions through circadian rhythms (Tordjman et al., 2017). This hormone has been linked to the circadian clock through oxidative stress due to its antioxidant properties. Due to its lipophilic characteristics, melatonin can cross biological barriers, such as the blood–brain and the placental barriers. Several studies suggest its potential to regulate endogenous antioxidant systems (Liu et al., 2019). Melatonin is produced from the essential amino acid tryptophan in the pineal gland of humans, but it is also found in microorganisms and plants, where it is known as "phytomelatonin." The concentration of melatonin in foods varies and has been reported in various food groups, including nuts, cereals, fruits and vegetables, coffee, green tea, products of animal origin, among others (Meng et al., 2017)

This hormone is essential in the clock system (Figure 3.4); however, the amount of physiologically produced melatonin decreases with age and may be related to the development of pathological conditions related to the interruption of the clock. This effect can be enhanced by administering melatonin-rich foods and increasing its circulating levels and total plasma antioxidant potential. However, evidence is lacking on the use of phytomelatonin, plant origin, or foods that contain it as a chronobiotic (Dufoo-Hurtado et al., 2020 and references therein). In this regard, evidence in humans suggests a beneficial effect of consuming spent coffee fiber (SCF) on markers of the circadian clock (improvement of sleep, physical activity, and chronotype) of people, suggesting that this effect could be due to the amount of phytomelatonin present in coffee; nevertheless, more studies are needed to demonstrate this hypothesis (Oseguera-Castro et al., 2019). It has recently been reported in an *in vitro* model that pistachios phytomelatonin is bioaccessible and permeable during its passage in the gastrointestinal tract, which suggests its potential bioavailability to exert its chronobiotic effect and alleviate health problems related to circadian alterations (Dufoo-Hurtado et al., 2021).

3.5 Current Trends and Perspectives

Chrononutrition as a subdiscipline of chronobiology has been consolidating for two decades. During this time, the empirical knowledge that certain rhythmic biological processes are linked to eating patterns and that some modifiers of the biological clock (e.g. herbal teas and coffee) reduce the probability of suffering from certain diseases has been supported by solid scientific evidence outlining its mechanisms at the cellular and systemic level. We have also witnessed progress in the understanding of the chemical biotransformation processes of some food bioactives of animal and plant origin, along with the discovery of the genetic and epigenetic mechanisms that govern them. Despite all this, studies in chrononutrition are still scarce and its recognition as an applied scientific discipline will be consolidated in the coming years. Nevertheless, studies published in chronobiotics nutrition provide guidelines to offer recommendations on alternative and/or complementary therapy to the already recognized chronobiotics.

Chronobiotics is slowly setting a foothold in mainstream product development. For example, two companies (Unilever and Microba) are collecting information on gut bacteria's role in regulating circadian rhythm, promoting sleep quality and the production of substances that aid and encourage sleep (Chu, 2021). Their initiative is based on emerging evidence on the link between gut microbiome and inflammation and sleep loss, circadian misalignment, affective disorders, and metabolic disease. Moreover, the gut phyla (Bacteroidetes and Firmicutes) positively associated with sleep efficiency influences both circadian rhythm and food intake thereby impacting sleep quality. InnoBev, a US-based start-up has introduced BioLift, a beverage featuring natural ingredients (guarana, ginkgo biloba, and elderberry) to synchronize with circadian rhythm by elevating focus, alertness, and performance. The energizing beverage apparently increases vigilance, improves cognitive function, delivers mental stimulation, and boosts the immune system. Givaudan Active Beauty released Synchronolight (gardenia fruit extract), an active cosmetic ingredient for skincare, designed to protect the skin from digital stress or artificial blue lights that impact

circadian rhythm. In chrononutrition, supplements with energetic properties such as cordyceps and fermented ginseng are promoted for morning consumption to help the body focus throughout the day (Nutrition Insight, 2020). Mantra Labs developed comprehensive biorhythm-matched products "Rise"([vitamins, hydration minerals, electrolytes nootropics), "Go" (fermented tea leaf caffeine), and "Rest" to address chrononutrition requirements for morning, afternoon, and evening, respectively (Masterson, 2020).

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