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Phenolic compounds and biological rhythms: Who takes the lead?

Javier Ávila-Román, Jorge R. Soliz-Rueda, Francisca Isabel Bravo, Gerard Aragonès, Manuel Suárez, Anna Arola-Arnal, Miquel Mulero, Maria-Josepa Salvadó, Lluís Arola, Cristina Torres-Fuentes *, Begoña Muguerza

Universitat Rovira i Virgili, Departament de Bioquimica i Biotecnologia, Nutrigenomics Research Group, 43007, Tarragona, Spain

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ABSTRACT

Background: Phenolic compounds are one of the most heterogeneous group of plant secondary metabolites with over 50,000 diverse molecules identified so far. Despite the low bioavailability of native forms, they have been shown to exert several beneficial effects against chronic diseases such as diabetes, cardiovascular disease, and neurodegenerative diseases. There are different factors that may affect their absorption and distribution in tissues, but the exact mechanisms remain unclear. Recently, the time of the day and the season of the year in which they are consumed have emerged as another factor that may significantly impact on their metabolism and bioactivities.

Scope and approach: This review emphasizes the importance of the interaction between phenolic compounds and biological rhythms and its impact on the bioactivities of these metabolites. This may have implications for the food industry as food rich in phenolic compounds may exert different effects depending on the time of consumption.

Key findings and conclusions: Phenolic compounds broad activity could be explained by their extensive transformation, including metabolization in the colon by the gut microbiota, which leads to the production of multitude of different metabolites. Biological rhythms play a significant role in this metabolism affecting their bioactivities and, at the same time, phenolic compounds may exert their effects by promoting homeostasis at a basal signalling level through interactions with the biological clock system. This is in accordance with the xenohormesis hypothesis, which explains that chemical cues synthetized by plants are able to allow animals to favourably adapt to changing environmental conditions.

1. Phenolic compounds

Dietary phenolic compounds have received tremendous scientific and consumers attention due to their roles in human health. These compounds are bioactive molecules obtained from plant-based foods such as fruits, nuts, seeds, leaves and roots, plant-derived beverages such as tea or wine, and algal-derived products (Del Rio et al., 2013; Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). They are an important class of plant secondary metabolites which play crucial physiological roles generally involved in the attraction of pollinators, the execution of structural functions, the protection against ultraviolet (UV) radiation and the defence of plants against microbial invasion and herbivores (Cutrim & Cortez, 2018; Sharma et al., 2019). Under abiotic stress conditions, such as drought, heavy metal, salinity, high/low temperature, and UV radiations, plants increase phenolic compounds synthesis, especially polyphenols, as a defence mechanism to cope with environmental unfavourable conditions (Sharma et al., 2019). This complex large group of phytochemicals is chemically characterized by the presence of at least one hydroxyl group in the structure bonded directly to an aromatic ring and can be classified in flavonoids (isoflavones, flavones, flavonols, flavanols, flavanones and anthocyanidins) and non-flavonoids (phenolic alcohols, phenolic acids, stilbenes and lignans) (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). Structurally phenolic compounds are very heterogeneous, and over 50,000 diverse molecules have been identified so far (Ziaullah & Rupasinghe, 2015)).

The study of these compounds may be challenging due to their

* Corresponding author.
E-mail addresses: franciscojavier.avila@urv.cat (J. Ávila-Román), jorgericardo.soliz@urv.cat (J.R. Soliz-Rueda), franciscaisabel.bravo@urv.cat (F.I. Bravo), gerard.aragones@urv.cat (G. Aragonès), manuel.suarez@urv.cat (M. Suárez), anna.arola@urv.cat (A. Arola-Arnal), miquel.mulero@urv.cat (M. Mulero), mariajosepa.salvado@urv.cat (M.-J. Salvadó), lluis.arola@urv.cat (L. Arola), cristina.torres@urv.cat (C. Torres-Fuentes), begona.muguerza@urv.cat (B. Muguerza).

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heterogenicity and variety, and the complexity of their matrices, and because they are easily oxidized. However, it became an emerging field of interest for the scientific community due to their strong antioxidant properties and capacity to neutralize free radicals. Indeed, they have demonstrated to be the main contributor for antioxidant effects in fruits, even superior to that of the vitamin C (Tsao, 2010). In the last years different studies have demonstrated that phenolic compounds are also able to exert different effects at molecular level including the modulation of nuclear receptors, miRNAs and enzymatic activity as well as epigenetic modifications affecting different signalling pathways (Pan, Lai, Wu, & Ho, 2013). In this regard, they are also of interest for different industry sectors such as food and nutraceutical. Moreover, when added to foods, their antioxidants properties delay the formation of toxic oxidation products, maintain nutritional quality, and extend the shelf-life of products (Grobelna, Anna; Kalisz et al., 2020; Grobelna et al, 2019a, 2019b; Kalisz et al., 2020; Shahidi & Yeo, 2018). In addition, these compounds can be also of interest for agriculture, in which some can be used as allelochemicals (Mousavi, Karami, Haghighi, Alizadeh, & Maggi, 2021) and biostimulants (Mazrou, 2019) as well as other chemicals such as azadirachtin, a limonoid terpenoid found in *Azadirachta indica*, which has shown to be potent insecticide in ecological agriculture (Kharwar et al., 2020).

Different beneficial effects of phenolic compounds consumption have been shown in several epidemiological studies, including anticancer, anti-inflammatory, antibacterial activities, analgesic, anti-allergic, and anti-Alzheimer's properties, which may help in the treatment and/or prevention of different chronic diseases such as diabetes, cardiovascular disease, and neurodegenerative diseases (García-Conesa & Larrosa, 2020; Luca et al., 2020; Shahidi & Yeo, 2018; Tsao, 2010). In addition, recent studies have shown that phenolic compounds from *Moringa oleifera* which protect this plant against stress factors, may have a potential pharmacological use due to their anti-inflammatory and anti-hypertensive effects in both experimental models and clinical trials (Oldoni et al., 2021; Ożarowski et al., 2021). These findings reveal the effects of phenolics to promote health and the relevance of studying their role in the metabolism. Nevertheless, despite this broad activity the phenolic compounds present in food have shown a low bioavailability (Manach et al., 2004). Indeed, different studies have revealed that phenolics bioavailability is affected by different external and internal host factors such as dose, length of the treatment, sex and age (D'Archivio, Filesi, Varì, Scazzocchio, & Masella, 2010). Host health status has also recently pointed out as other factor influencing the bioavailability of phenolic compounds (Margalef, Pons, Iglesias-Carres, Bravo, et al., 2017; Margalef, Pons, Iglesias-Carres, Quiñones, et al., 2017). Due to this low bioavailability, only a small part of the ingested phenolics is absorbed by the small intestine (5–10%) while the rest

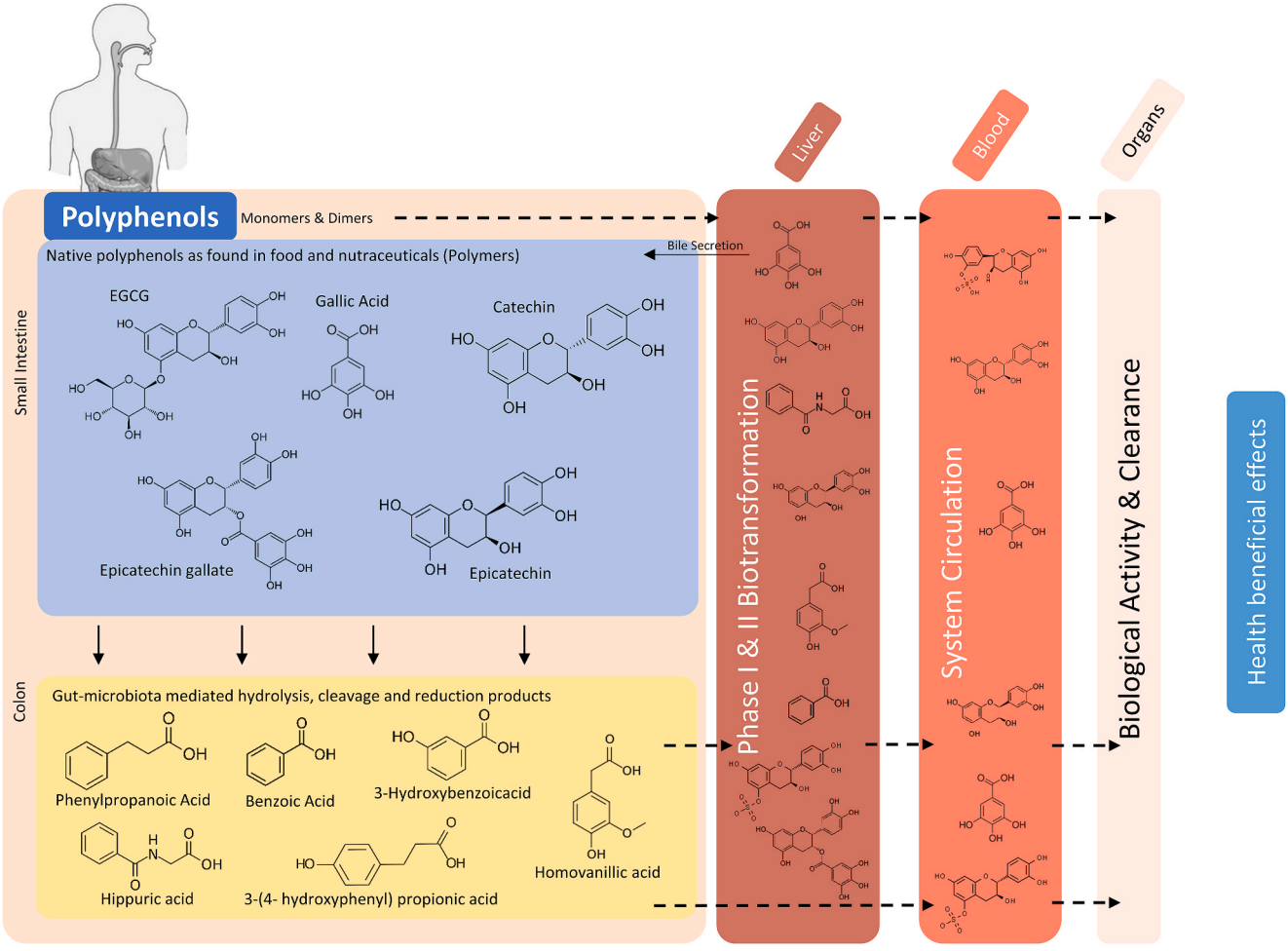

Fig. 1. Metabolism of a grape seed proanthocyanidin extract (GSPE). Tissue and systemic distribution of the main polyphenol metabolites identified by HPLC-MS/MS in Wistar rats after oral administration of GSPE (1 g/kg). Part of the native polyphenols found in the extract are absorbed at small intestine level and distributed to different tissues including the liver. Other native polyphenols reach the colon where they are metabolized by the gut microbiota, via deglycosylation, dehydroxylation and demethylation reactions, and absorbed for their distribution. In the liver, polyphenols metabolites undergo further biotransformation by glucuronidation, sulfation and/or methylation reactions. In addition, these metabolites may be transferred back into the intestine through the enterohepatic cycle. Adapted from (Guerrero et al., 2013; Margalef et al., 2015a, 2015b).

(90–95%) reach the colon. In the small intestine they are transformed by conjugation reactions including glucuronidation, sulfation and/or methylation and absorbed by the enterocytes. In the colon they are metabolized by the gut microbiota (via deglycosylation, dehydroxylation and demethylation reactions) and absorbed by the colonocytes (Ozdal et al., 2016). The absorbed phenolic compounds and their derived metabolites are transported to the liver by the portal circulation and they are further metabolized by the above-mentioned conjugation reactions. In addition, these metabolites may be transferred back into the intestine through the enterohepatic cycle (Van Duynhoven et al., 2011). Finally, the absorbed phenolic metabolites are transported through the systemic circulation to the different tissues and organs (Cardona, Andrés-Lacueva, Tulipani, Tinahones, & Queipo-Ortuño, 2013). This complex absorption and metabolism process is illustrated in Fig. 1, taking as example the case of a grape seed proanthocyanidin extract (GSPE) in which our group have extensive experience. Therefore, phenolic compounds are subject to an extensive transformation leading to the production of several different metabolites, which explains the large inter-individual variability in response to their consumption.

In addition to the factors mentioned above, biological rhythms have been shown to influence the activity of bioactive compounds, including phenolic compounds (Arola-Arnal et al., 2019). In this context, the time of the day or the season of the year should be taken into account when investigating the bioactivities of these compounds. This has led to the development of a new research area called chrononutrition. Moreover, it has been proposed that animals are able to favourably adapt to changing environmental conditions through the consumption of chemical cues synthetized by plants, which is known as xenohormesis (Howitz & Sinclair, 2008). According to this hypothesis, plants experiencing mild stress activate their own cellular defences by synthetizing phytochemicals such as phenolic compounds that, when they are incorporated through the diet, will allow mammals to adjust their metabolism in anticipation of adverse conditions promoting their survival. Thus, phenolic compounds and especially polyphenols may provide physiological and metabolic signals facilitating the adaptation to the environment (Baur & Sinclair, 2008). Hence, we hypothesize that phenolic compounds may exert their beneficial effects promoting homeostasis maintenance at a basal signalling level, including interactions with the biological clock system.

2. Biological rhythms

Biological rhythms are periodic variations in the intensity of biological processes and vital functions of living organisms caused by different factors such as the rotation of the Earth around its axis (circadian cycle) and its translation around de sun (seasonal cycle). They allow for the adjustment of the organisms to environmental changes such as food availability or predator activity. Thus, circadian and seasonal rhythms enable organisms to optimize the metabolism and energy utilization to sustain life adapting their behaviour and physiology to the appropriate time of the day or of the year respectively. In this sense, physiological and behavioural systems of mammals such as sleep-wake cycle, cardiovascular activity, endocrine system, blood pressure, body temperature, renal activity, gastrointestinal tract activity and hepatic metabolism are regulated to a greater or lower extent by circadian rhythms (Claustrat, Brun, & Chazot, 2005; Levi & Schibler, 2007; Ohdo, 2003). These time-of-day-dependent rhythms are due to changes in energy expenditure and nutrient utilization that occur in cycles of 24 h (McGinnis & Young, 2016). The central clock regulatory system is located in the hypothalamic suprachiasmatic nucleus (SCN), which contains 10,000–15,000 neurons. This master clock can work autonomously, without any external input, but can be reprogrammed by external environmental cues named *zeitgebers* such as light, the most important one, which is perceived by the retina through the retinohypothalamic tract (Reppert & Weaver, 2002). Central clock provides signals, via the autonomic nervous system or circulating humoral factors including melatonin and cortisol (Dibner, Schibler, & Albrecht, 2009), to several peripheral oscillators to maintain rhythmicity and to ensure temporally coordinated physiology. These peripheral clocks are present in almost all other mammalian tissues, including liver, muscle, pancreas, and adipose tissue, where they maintain circadian rhythms and regulate tissue-specific gene expression and functionality. Peripheral oscillators are also regulated by behavioural signals such as physical activity and, most notably, fasting/feeding states (Levi & Schibler, 2007). Therefore, although circadian clock regulates multiple metabolic pathways, metabolites availability and feeding behaviour can also influence rhythms, being two systems that are reciprocally regulated. Thus, food entrains the liver clock, whereas light acts through the brain clock to control feeding time. In mammals, the circadian machinery is an intracellular mechanism sharing the same molecular components in SCN neurons and peripheral cells. The central feature of this molecular rhythmicity is the transcription–translation autoregulatory feedback loop which cycles with a periodicity of 24 h (Ohdo, 2003). The transcriptional activators of this feedback system are the circadian locomotor output cycles kaput (CLOCK) and the brain and muscle Arnt-like protein-1 (BMAL1). CLOCK and BMAL1 form a heterodimer that can activate the transcription upon binding to E-box (5′-CACGTG -3′) and E-box-like sequences found in the promoters of circadian-responsive genes. Its target factors Period (PER) and Cryptochrome (CRY) are rhythmically accumulated in the cytoplasm, oligomerize after reaching an appropriate concentration and translocate to the nucleus where interact with *Clock* and *Bmal1* inhibiting their own transcription. All the above mentioned clock elements exhibit a 24 h transcriptional oscillation in SCN cells and peripheral tissues, except for *Clock* that has been shown not to oscillate in the SCN (Dunlap, 1999; Lowrey & Takahashi, 2004; Reppert & Weaver, 2002; Young & Kay, 2001).

These clock genes are also responsible for circannual rhythms modulation. In peripheral organs, circannual rhythmicity is not self-sustained and requires maintenance by photoperiod signals. These signals are recognised in the retina and transmitted to the pineal gland by multi-synaptic neuronal pathways. The pineal gland integrates these photoperiod signals and regulates the production of melatonin, which is rhythmically produced at night (Korf, 2018). Thus, melatonin signals encode night length. Importantly, melatonin can regulate many physiological factors in humans, and those include immunity, metabolism and body temperature. Thus, melatonin controls the rhythmicity and seasonality of body physiology (Claustrat et al., 2005).

Biological rhythms may impact on the physiology and metabolism of the organism by through different mechanisms including: 1) modulation of the expression of enzymes involved in the rate-limiting steps of metabolic pathways, 2) interaction of the clock machinery with proteins such as nuclear receptors and nutrient sensors, and 3) regulation of metabolites levels (Sahar & Sassone-Corsi, 2012). However, this rhythmicity can be desynchronized from the central circadian clock by different factors, including environmental conditions (light-dark cycles), lifestyle and behavioural choices (work schedules, eating patterns, and social jet lag) or the presence of diseases. A large body of studies has extensively shown that this chronic circadian misalignment leads to serious health consequences, increasing the risk of developing obesity, metabolic and cardiovascular diseases (CVD), cancer or diabetes (Cannizzaro et al., 2020; Guerrero-Vargas, Espitia-Bautista, Buijs, & Escobar, 2018; Johnston, Ordovás, Scheer, & Turek, 2016; Kecklund & Axelsson, 2016). In this sense, many of them have been focused on evaluating the effect of circadian disruption on shift workers, which frequently experience circadian misalignment due to alterations of sleep-wake and fast-feeding timings.

Especially remarkable, the changes in dietary habits observed in last decades have also a high influence on the onset of these disruptions, as hypercaloric diets rich in free sugars and high-fat content are related with the development of metabolic diseases and related comorbidities. Taking into consideration all this evidence that link disruption of biological rhythms and health diseases, in their recent review Zimmet et al.

(2019) introduced the term "circadian syndrome", defining it as the underlying aetiological factor of metabolic syndrome. These authors describe this circadian syndrome as the joint of the metabolic syndrome cluster and their comorbidities including sleep apnea, depression and non-alcoholic fatty liver disease (Zimmet et al., 2019).

3. Phenolic compounds and biological rhythms modulation

The bioactivity of compounds is usually determined without taking into account the time of their administration. However, as discussed above, it seems evident that biological rhythms must be considered as many physiological and metabolic processes present time-dependent oscillations. Therefore, the time of the day or the season of the year in which dietary compounds are consumed must be a main determinant of the effect of diet on health (Johnston et al., 2016). This concept led to the development of the chrononutrition field, but unfortunately, there are not many studies evaluating the effects of the timing of the administration of bioactive components on their bioavailability and efficacy. Those that have been carried out so far are mainly focused on the study of foods or nutraceuticals rich in melatonin, an important component of the internal clock, or its precursors tryptophan and/or serotonin. For example, in a study using tryptophan enriched infant milk formulas to improve the development of the wake-sleep rhythms, the infants receiving the enriched formula during dark time showed improvements in the sleep parameters studied, in comparison with those receiving the enriched formula during light time or receiving standard infant commercial milk. The urinary metabolites of serotonin suggest that the observed improvements were due to an increased use of serotonin to melatonin synthesis (Aparicio et al., 2007). In other studies, the consumption twice a day as the lunch and dinner desserts of either a diet enriched with Jerte Valley cherries and a Jerte Valley cherry-based nutraceutical product, both rich in melatonin, serotonin, and tryptophan (González-Gómez et al., 2009), improved the antioxidant status of young, middle-aged, and elderly individuals (Garrido et al., 2010; Garrido, González-Gómez et al., 2013). The timing of the meal was critical for achieving the beneficial effects of these dietary interventions since serotonin and melatonin have opposite circadian rhythms. Thus, consumption of cherries at lunchtime allowed for an increase in the diurnal circulating serotonin concentration which indirectly also led to an increase in the nocturnal circulating melatonin concentration by enhancing the amount of serotonin available to be converted into melatonin at night (Garrido, Terrón, & Rodríguez, 2013). Moreover, this is a bidirectional interaction, and not only the biological rhythms may affect dietary components metabolism and functionality but also the other way around. Indeed, in the case of phenolic compounds, it has been shown that they are able to impact on the clock system, leading to changes in gene expression.

3.1. Biological rhythms impact on phenolic compounds activity

As discussed before, biological rhythms may significantly impact on dietary compounds bioavailability and activities. In the case of phenolic composition it has been shown that its bioavailability follows endogenous circadian rhythms inducing changes in its antioxidant properties (Soengas, Cartea, Velasco, & Francisco, 2018). Moreover, their effectivity has been suggested to be closely related to the circadian rhythm of many physiological processes. Regarding glucose homeostasis it is known that glucose metabolism is tightly regulated in a diurnal rhythm based on the external light-dark cycle (Challet, 2013; Johnston, 2014) and internal feeding-fasting cycles (Al-Naimi, Hampton, Richard, Tzung, & Morgan, 2004; Kalsbeek, La Fleur, & Fliers, 2014). Thus, the misalignment of this feed-fasted state could be related to the predisposition to suffer from certain pathologies such as T2D or CVD, which have been observed especially in shift-working people (Al-Naimi et al., 2004; Pan, Schernhammer, Sun, & Hu, 2011). Several studies have reported the diurnal and/or nocturnal effect of phenolic compounds on specific physiological contexts. In this regard, our group has reported the ability of GSPE on the modulation of the circadian rhythm of liver clock-core and clock-controlled genes, which were dependent on the administration time (ZT0, at the beginning of the light phase *vs*. ZT12, at the beginning of the dark phase) (Ribas-Latre et al., 2015). In particular, oral administration of GSPE to male Wistar rats led to increased ratio of hepatic acetylated BMAL1 only at ZT12. In addition, this research pointed out that nicotinamide phosphoribosyl transferase (NAMPT), the rate limiting enzyme in nicotinamide adenine dinucleotide -NAD-biosynthesis) and NAD were important molecular targets of GSPE in the liver. In this regard, GSPE was able to modulate the levels of NAMPT and NAD in opposite ways depending on its administration time (reducing their levels in the diurnal treatment and increasing their levels in the nocturnal treatment). In consequence, this polyphenolic extract could act as a hepatic adaptation factor through the improvement of the energetic profile as well as through the increase of mitochondrial functional and oxidation at night, when rats are active. Finally, it was concluded that BMAL1 acetylation pattern, which was dependent on the GSPE administration time, could explain the *Nampt* overexpression and the following NAD peak in the liver, only when the polyphenol extract was administered at night. Moreover, in another study, GSPE showed different effects depending on the administration time in male Wistar rats. In this study, when administrated at ZT0 (light on), GSPE was able to delay the diurnal decrease in melatonin levels and altered the oscillations of some metabolites in plasma as well as *Bmal1* and *Nampt* expression pattern in the hypothalamus. However, when administrated at ZT12 (light off) no effects were observed (Ribas-Latre, Del Bas, Baselga-Escudero, Casanova, Arola-Arnal, Salvadó, Arola, et al., 2015). In addition, acute resveratrol (RSV) administration in male Wistar rats synchronized with a 12-h dark-light cycle, showed opposite effects on lipoperoxidation tissue level depending of the time of the day, being pro-oxidant when administered during light span and antioxidant when administered during the night-time (Gadacha et al., 2009). More concisely, this research evaluated the dosing-time dependency of acute RSV administration on lipoperoxidation levels in several male rat tissues (heart, liver, and kidney). A powerful antioxidant effect in these tissues was found when RSV was administered during the active phase (at dark). However, when administered during the rest phase (at light), RSV exerted pro-oxidant effects in the three organs, but in absence of any harmful effect at the tested dose. Authors indicated that this opposite effect of RSV depending on the administration time could be due to circadian changes in basal level of superoxide dismutase (SOD) isoforms and after resveratrol treatment in several organs. On the other hand, it has been demonstrated that a single-dose of a polyphenol-rich extract from the algae *Fucus vesiculosus* is able to slightly reduce the elevated postprandial blood glucose responses in the evening in healthy women (Murray, Dordevic, Ryan, & Bonham, 2019). Another study in young men evaluated the effects of timing of an acute catechin-rich green tea ingestion on postprandial glucose metabolism (Takahashi et al., 2019). The main finding of this study was that the acute ingestion of catechin-rich green tea reduced postprandial plasma glucose concentrations, in the evening but not in the morning.

In addition to circadian rhythms, circannual rhythms may also influence phenolics bioavailability and functionality. In this context, our group has recently shown that exposure of Fischer 344 rats to distinct photoperiods influences the bioavailability of red grape polyphenols (Iglesias-Carres et al., 2019). Moreover, hypothalamic leptin sensitivity was influenced by polyphenol-rich seasonal fruits (cherry and grape), in a photoperiod-dependent manner in Fischer 344 rats (Ibars et al., 2018). Thus, a significant increased hypothalamic gene expression of leptin receptor isoform B (*Obrb*) was observed only when cherries were consumed in short-day photoperiod. In addition, hypothalamic pro-opiomelanocortin (*Pomc*) expression, which is under leptin regulation, was significantly increased by grapes and cherries intake only when consumed in the SD photoperiod, indicating a clear photoperiod effect. Furthermore, consumption of polyphenol-rich fruit out of season

led to metabolism disruption, including lipid and glucose homeostasis, in both standard and cafeteria diet-fed rats (Mariné-Casadó et al., 2019) and causes changes in the white adipose tissue gene expression and in its morphology to a phenotype prone to fat accumulation (Gibert-Ramos, Crescenti, & Salvadó, 2018). Thus, cherry consumption for example, which is a fruit characteristic of long photoperiod, led to increased glycemia and insulinemia when consumed in short photoperiod by obese rats, and led to enhanced whole-body lipid utilization, resembling the substrate oxidation pattern observed in the animals exposed to 18 h of light. Taken all together, the most optimum phenolics profile in plant products should be in accordance with their seasonality and may also vary depending on the time of the day. Hence, their consumption in the wrong time may contribute to misleading signals promoting the development of metabolic diseases such as metabolic syndrome and obesity (Arola-Arnal et al., 2019). Further studies are needed to elucidate the mechanisms involved and the connection between specific phenolic compounds from seasonal foods and metabolism according to the period of the year.

On the other hand, gut microbiota has been postulated as one of the main elements in maintaining biological rhythms. Indeed, germ-free mice exhibited impaired circadian clock gene expression, despite the existence of light and dark signals (Leone et al., 2015). Moreover, diurnal and seasonal oscillations in gut microbes have been described (Carey, Walters, & Knight, 2013; R. M. Voigt, Summa, et al., 2016). In addition, mutations of the circadian protein CLOCK promotes intestinal dysbiosis (Robin M. Voigt, Summa, et al., 2016). Hence, the interaction between phenolic compounds and biological rhythms may be at least partially mediated by the gut microbiota. Thus, intestinal microbiota oscillations due to biological rhythms may affect to phenolic compounds metabolism and transformation in the colon and, therefore, leads to the production of different derived metabolites with different functionalities. Indeed, there have been studies that have shown evidence of this interaction between polyphenols-gut microbiota and circadian rhythms (Guo, Ho, Zhang, Cao, Wang, & Shao et al., 2019; Guo, Song, Ho, Zhang, Zhang, & Cao, et al., 2019; Man, Xia, Daiber, & Li, 2020).

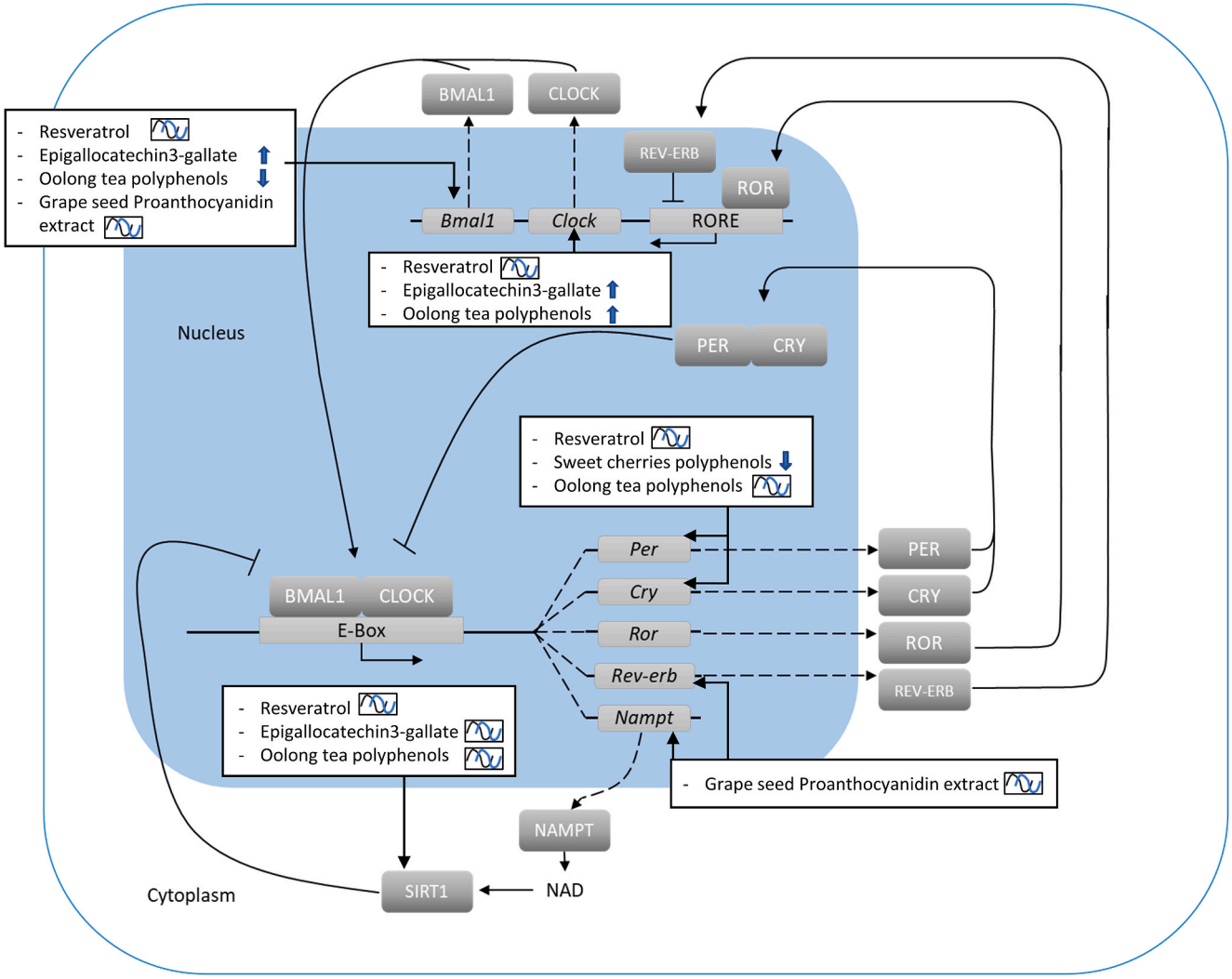

Fig. 2. Phenolic modulation of circadian intracellular machinery. This mechanism, which shares the same components in suprachiasmatic nucleus (SCN) neurons and peripheral cells, is characterized by the transcription-translation autoregulatory feedback loop in 24 h. The circadian locomotor output cycles kaput (CLOCK) and the brain and muscle Arnt-like protein-1 (BMAL1) are the major components. CLOCK-BMAL1 heterodimer can active the transcription of circadian-responsive genes upon binding to E-box sequences found in the promoters. Its target factors Period (PER) and Cryptochrome (CRY) are rhythmically accumulated in the cytoplasm, where oligomerize once reached an appropriate concentration and migrate into the nucleus interacting with Clock and Bmal1 inhibiting their own transcription. Multitude phenolic compounds or products have shown to regulate the pattern of the circadian rhythmicity acting in specific points of the intracellular machinery.

3.2. Phenolic compounds effects on biological rhythms

As mentioned above, dietary compounds may influence biological rhythms by modulating clock genes expression. In fact, nutritional challenges have been shown to affect the clock system (Eckel-Mahan et al., 2013). In this regard, in addition to macronutrients, the capability of several bioactive compounds to act in the modulation of clock genes is currently under study by the scientific community.

Indeed, phenolic compounds can function as *zeitgebers* for this molecular clock machinery regulating these genes expression (Fig. 2). This was first evidenced in 2008 (Oike & Kobori, 2008) by an *in vitro* study with RSV, which was able to regulate circadian clock genes in Rat-1 fibroblast cells. These findings support the potential interaction between phenolics functionality and circadian rhythms, which is of increasing research interest. In this sense, and regarding *in vitro* studies, several approaches have been done to disrupt circadian oscillations of clock genes by applying oxidative stress (H_2O_2, acrylamide) or metabolic (free fatty acids) stimuli on human hepatoma carcinoma cells (HepG2) as well as on primary hepatocytes. In such situations, the subsequent application of several types of phenolic compounds (e.g. RSV, Cichoric acid (CA), Green tea polyphenols) satisfactorily readdressed the misled circadian rhythm (R. Guo et al., 2018; Qi et al., 2018; Tan et al., 2019). Interestingly, these effects were linked to others beneficial effects of phenolic compounds including antioxidant, anti-inflammatory or anti-steatosis effects, among others. Additionally, the role of the central master clock in mediating the effects of phenolics has been investigated by knocking-down the regulator genes *Bmal1* and *Cry* using small interfering RNA (siRNA). This silencing, partially abrogated the beneficial effects of phenolic compounds, strengthening in consequence the pivotal role of the clock machinery in mediating these effects (R. Guo et al., 2018; Qi et al., 2018; Tan et al., 2019). For instance, CA regulated the circadian rhythm expressions of clock genes and, *Bmal1* silencing inhibited the effects of CA on lipid drop accumulation by downregulation of the p-Akt/Akt pathway and elevation of fatty acid synthase and acetyl coenzyme A carboxylase protein and mRNA levels and in HepG2 cells (R. Guo et al., 2018). A similar approach was used for studying the beneficial role of RSV on acrylamide oxidative damage. This study showed that RSV-mediated activation of Nrf2/NQO-1, which are essential antioxidant cell modulators, disappeared after knocking down *Bmal1*, indicating that RSV is able to restore the cellular redox status in a *Bmal1*-dependent manner (R. Guo et al., 2018). In consequence, these studies have contributed to a better understanding of the interaction between phenolic compounds and circadian clock and its influence on oxidative stress, inflammation response as well as metabolic disorders. Furthermore, other authors have shown that some biological processes that follow circadian oscillations, such as triacylglycerol secretion (Del Bas et al., 2008) and microRNA expression (Arola-Arnal & Bladé, 2011), are strongly modulated by phenolic products such as GSPE (Arola-Arnal & Bladé, 2011; Del Bas et al., 2008), cocoa proanthocyanidin extract (CPE) and pure epigallocatechin gallate isolated from green tea (EGCG) (Arola-Arnal & Bladé, 2011). Interestingly, GSPE is also able to mimic melatonin action by upregulating BMAL1 expression, and consequently it is able to modulate the circadian rhythm of clock genes in HepG2 cells (Ribas-Latre, Del Bas, Baselga-Escudero, Casanova, Arola-Arnal, Salvadó, Bladé, et al., 2015). Hence, although GSPE did not affect the percentage of rhythmicity of any studied clock gene (*Bmal1*, *Clock*, *Rorα*, *REV-Erbα*, *Per2* and *Cry1*), it increased the amplitude of REV-ERBα. On the other hand, GSPE significantly shifted the acrophase of both the core clock and clock-controlled genes. Additionally, the altered gene expression of *Bmal1* and *Rorα* clearly suggested both genes as targets of GSPE. Finally, it was also shown that the molecular mechanisms by which melatonin and GSPE induced the overexpression of *Bmal1* were different, being dependent on the melatonin receptor 1 (MT1) in the case of melatonin but independent from this receptor in the case of GSPE. In this regard, by using an elegant approach, Shinozaji et al. (Shinozaki et al., 2017) showed a remarkable effect of several flavonoids on circadian rhythms. For this purpose, they tested the modifications in the circadian clock amplitude, period, and phase induced by the addition of polyphenols (transiently or continuously) in embryonic fibroblasts from PER2:LUCIFERASE (PER2:LUC) mice. They discovered that the transient treatment with some flavonoids induced a phase delay of the PER2:LUC rhythm at the down slope phase. On the other hand, the continuous application of nobiletin and tangeretin, which are polymethoxy flavonoids, increased the amplitude and lengthened the period of the PER2:LUC rhythm. Interestingly, this nobiletin-induced phase delay was dependent on ERK activity, because the co-treatment with the ERK inhibitor U0126 abrogated such nobiletin effect.

The influence of phenolic compounds on the circadian rhythm modulation has also been addressed *in vivo*. For example, it has been shown that there is a significant coordination between circadian clock machinery and hepatic metabolism (Zhou et al., 2014). In particular, it was shown that CLOCK/BMAL1 regulates circadian change of mouse hepatic insulin sensitivity by SIRT1. Importantly, RSV abolished the negative effect of constant darkness on SIRT-1 activity, as well as on glucose and insulin intolerance (Zhou et al., 2014). This suggests that RSV could be an interesting option for combating metabolic disorders under circadian misalignment conditions thorough modulating the circadian regulation of SIRT1. Additionally, it has also been shown in the adipose tissue that RSV reverses the alteration induced by high-fat diet (HFD) feeding in the expression of *Rev-Erbα* in male Wistar rats (Miranda et al., 2013). Furthermore, another study showed that RSV was able to restore the circadian rhythmic disorder of lipid metabolism induced by HFD in male C57BL/6 mice. Specifically, RSV modulated the expression rhythm of clock genes (*Clock*, *Bmal1* and *Per2*) and clock-controlled lipid metabolism related genes (*Sirt1*, *Pparγ*, *Srebp-1c*, *Acc1* and *Fas*). In consequence, RSV was able to restore the circadian misalignment due to HFD (Sun et al., 2015). Similar studies have been done with other phenolic compounds like EGCG (Mi et al., 2017). Other studies have addressed the effect of GSPE on molecular clock machinery in a healthy *vs*. obesity scenario. In this regard, the oral administration of GSPE for 21 days to healthy male Wistar rats induced the overexpression of core clock genes in a dose-dependent manner. Additionally, the acetylated level of BMAL1, which is a SIRT1 target, also increased in a dose dependent manner in the liver and mesenteric white adipose tissue (WAT) of these animals (Ribas-Latre et al., 2015). In the same study, the administration of GSPE to cafeteria diet-fed obese rats was able to counteract the perturbations induced by obesity in the clock genes mainly in the liver and gut, but surprisingly the polyphenol rich extract was less effective in normalizing the clock gene disruption in WAT. This reinforces the concept that the clock machinery is also an important target for phenolic compounds in its already known protective effect against obesity (Ribas-Latre et al., 2015).

4. Conclusions

Biological rhythms must be considered when studying phenolic compounds as they have been demonstrated to significantly impact on their bioavailability and functionality. Moreover, despite to the complex absorption and metabolism process to which dietary phenolic compounds are subjected, leading to the production of thousands of different metabolites, they have been shown to exert several beneficial effects. This broad range of activity may be due to their capability to promote homeostasis at a basal signalling level through interactions with the biological clock system. Indeed, a multitude of studies has shown that circadian and circannual rhythms may affect their absorption and metabolism, impacting their bioactivity and functionality. Moreover, dietary phenolic compounds have been proven to exert many beneficial metabolic and physiological effects in different experimental studies by modulating genes related to the clock machinery and associated signalling pathways. The studies discussed here support the xenohormesis hypothesis, which postulates that stress signalling molecules produced

by plants, such as phenolic compounds, allows mammals to better cope with the imbalances produced throughout their life. Further studies are needed in order to elucidate the specific mechanisms involved in this interesting two-way phenolic compounds-biological rhythms interaction.

CRediT authorship contribution statement

JAR, JSR, FIB, GA, MS, AA, MM, MJS, LA, CTF and BM: writing. JAR, CTF and BM: reviewing & editing; JSR: artwork.

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References

Al-Naimi, S., Hampton, S. M., Richard, P., Tzung, C., & Morgan, L. M. (2004). Postprandial metabolic profiles following meals and snacks eaten during simulated night and day shift work. *Chronobiology International, 21*(6), 937–947. https://doi.org/10.1081/CBI-200037171

Aparicio, S., Garau, C., Esteban, S., Nicolau, M. C., Rivero, M., & Rial, R. V. (2007). Chrononutrition: Use of dissociated day/night infant milk formulas to improve the development of the wake-sleep rhythms. Effects of tryptophan. *Nutritional Neuroscience, 10*(3–4), 137–143. https://doi.org/10.1080/10284150701455916

Arola-Arnal, A., & Bladé, C. (2011). Proanthocyanidins modulate MicroRNA expression in human HepG2 cells. *PloS One, 6*(10), Article e25982. https://doi.org/10.1371/journal.pone.0025982

Arola-Arnal, A., Cruz-Carrión, Á., Torres-Fuentes, C., Ávila-Román, J., Aragonès, G., Mulero, M., et al. (2019). Chrononutrition and polyphenols: Roles and diseases. *Nutrients, 11*(11), 2602. https://doi.org/10.3390/nu11112602

Baur, J. A., & Sinclair, D. A. (2008). What is xenohormesis? *American Journal of Pharmacology and Toxicology, 3*(1), 149–156. https://doi.org/10.3844/ajptsp.2008.152.159

Cannizzaro, E., Cirrincione, L., Mazzucco, W., Scorciapino, A., Catalano, C., Ramaci, T., et al. (2020). Night-time shift work and related stress responses: A study on security guards. *International Journal of Environmental Research and Public Health, 17*(2), 1–9. https://doi.org/10.3390/ijerph17020562

Cardona, F., Andrés-Lacueva, C., Tulipani, S., Tinahones, F. J., & Queipo-Ortuño, M. I. (2013). Benefits of polyphenols on gut microbiota and implications in human health. *Journal of Nutritional Biochemistry, 24*(8), 1415–1422. https://doi.org/10.1016/j.jnutbio.2013.05.001

Carey, H. V., Walters, W. A., & Knight, R. (2013). Seasonal restructuring of the ground squirrel gut microbiota over the annual hibernation cycle. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 304*(1), R33–R42. https://doi.org/10.1152/ajpregu.00387.2012

Challet, E. (2013). Circadian clocks, food intake, and metabolism. In *Progress in molecular biology and translational science, 119* pp. 105–135). Elsevier B.V. https://doi.org/10.1016/B978-0-12-396971-2.00005-1.

Claustrat, B., Brun, J., & Chazot, G. (2005). The basic physiology and pathophysiology of melatonin. *Sleep Medicine Reviews, 9*(1), 11–24. https://doi.org/10.1016/j.smrv.2004.08.001

Cutrim, C. S., & Cortez, M. A. S. (2018). A review on polyphenols: Classification, beneficial effects and their application in dairy products. *International Journal of Dairy Technology, 71*(3), 564–578. https://doi.org/10.1111/1471-0307.12515

D'Archivio, M., Filesi, C., Varì, R., Scazzocchio, B., & Masella, R. (2010). Bioavailability of the polyphenols: Status and controversies. *International Journal of Molecular Sciences, 11*(4), 1321–1342. https://doi.org/10.3390/ijms11041321

Del Bas, J. M., Ricketts, M. L., Baiges, I., Quesada, H., Ardevol, A., Salvadó, M. J., et al. (2008). Dietary procyanidins lower triglyceride levels signaling through the nuclear receptor small heterodimer partner. *Molecular Nutrition & Food Research, 52*(10), 1172–1181. https://doi.org/10.1002/mnfr.200800054

Del Rio, D., Rodriguez-Mateos, A., Spencer, J. P. E., Tognolini, M., Borges, G., & Crozier, A. (2013). Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxidants and Redox Signaling, 18*(14), 1818–1892. https://doi.org/10.1089/ars.2012.4581

Dibner, C., Schibler, U., & Albrecht, U. (2009). The mammalian circadian timing system: Organization and coordination of central and peripheral clocks. *Annual Review of Physiology, 72*, 517–549. https://doi.org/10.1146/annurev-physiol-021909-135821

Dunlap, J. C. (1999). *Molecular Bases for Circadian Clocks Review review word for the late 80s and early 90s would have. In Cell. 96*.

Eckel-Mahan, K. L., Patel, V. R., De Mateo, S., Orozco-Solis, R., Ceglia, N. J., Sahar, S., et al. (2013). Reprogramming of the circadian clock by nutritional challenge. *Cell, 155*(7), 1464–1478. https://doi.org/10.1016/j.cell.2013.11.034

Gadacha, W., Ben-Attia, M., Bonnefont-Rousselot, D., Aouani, E., Ghanem-Boughanmi, N., & Touitou, Y. (2009). Resveratrol opposite effects on rat tissue lipoperoxidation: Pro-oxidant during day-time and antioxidant at night. *Redox Report, 14*(4), 154–158. https://doi.org/10.1179/135100009X466131

García-Conesa, M.-T., & Larrosa, M. (2020). Polyphenol-rich foods for human health and disease. *Nutrients, 12*(2), 400. https://doi.org/10.3390/nu12020400

Garrido, M., González-Gómez, D., Lozano, M., Barriga, C., Paredes, S. D., & Rodríguez, A. B. (2013). Characterization and trials of a Jerte Valley cherry product as a natural antioxidant-enriched supplement. *Italian Journal of Food Science, 25*(1), 90–97.

Garrido, M., Paredes, S. D., Cubero, J., Lozano, M., Toribio-Delgado, A. F., Munoz, J. L., et al. (2010). Jerte Valley cherry-enriched diets improve nocturnal rest and increase 6-sulfatoxymelatonin and total antioxidant capacity in the urine of middle-aged and elderly humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 65A*(9), 909–914. https://doi.org/10.1093/gerona/glq099

Garrido, M., Terrón, M. P., & Rodríguez, A. B. (2013). Chrononutrition against oxidative stress in aging. In *Oxidative medicine and cellular longevity, 2013*Hindawi Limited. https://doi.org/10.1155/2013/729804.

Gibert-Ramos, A., Crescenti, A., & Salvadó, M. (2018). Consumption of cherry out of season changes white adipose tissue gene expression and morphology to a phenotype prone to fat accumulation. *Nutrients, 10*(8), 1102. https://doi.org/10.3390/nu10081102

González-Gómez, D., Lozano, M., Fernández-León, M. F., Ayuso, M. C., Bernalte, M. J., & Rodríguez, A. B. (2009). Detection and quantification of melatonin and serotonin in eight Sweet Cherry cultivars (Prunus avium L.). *European Food Research and Technology, 229*(2), 223–229. https://doi.org/10.1007/s00217-009-1042-z

Grobelna, A., Kalisz, S., & Kieliszek, M. (2019). Effect of processing methods and storage time on the content of bioactive compounds in blue honeysuckle berry purees. *Agronomy, 9*(12), 860. https://doi.org/10.3390/agronomy9120860

Grobelna, A., Kalisz, S., & Kieliszek, M. (2019). The effect of the addition of blue honeysuckle berry juice to apple juice on the selected quality characteristics, anthocyanin stability, and antioxidant properties. *Biomolecules, 9*(11), 744. https://doi.org/10.3390/biom9110744

Grobelna, A., Kalisz, S. M., Liviu, K., & Giurgiulescu. (2020). Blue Honeysuckle Berry (lonicera caerulea l.), as raw material, is particularly predisposed to the production of functional foods. *Carpathian Journal of Food Science and Technology*, 144–155. https://doi.org/10.34302/crpjfst/2020.12.3.12

Guerrero-Vargas, N. N., Espitia-Bautista, E., Buijs, R. M., & Escobar, C. (2018). Shift-work: Is time of eating determining metabolic health? Evidence from animal models. *Proceedings of the Nutrition Society, 77*(3), 199–215. https://doi.org/10.1017/S0029665117004128

Guerrero, L., Margalef, M., Pons, Z., Quiñones, M., Arola, L., Arola-Arnal, A., et al. (2013). Serum metabolites of proanthocyanidin-administered rats decrease lipid synthesis in HepG2 cells. *Journal of Nutritional Biochemistry, 24*(12), 2092–2099. https://doi.org/10.1016/j.jnutbio.2013.08.001

Guo, T., Ho, C. T., Zhang, X., Cao, J., Wang, H., Shao, X., et al. (2019). Oolong tea polyphenols ameliorate circadian rhythm of intestinal microbiome and liver clock genes in mouse model. *Journal of Agricultural and Food Chemistry, 67*(43), 11969–11976. https://doi.org/10.1021/acs.jafc.9b04869

Guo, T., Song, D., Ho, C. T., Zhang, X., Zhang, C., Cao, J., et al. (2019). Omics analyses of gut microbiota in a circadian rhythm disorder mouse model fed with oolong tea polyphenols. *Journal of Agricultural and Food Chemistry, 67*(32), 8847–8854. https://doi.org/10.1021/acs.jafc.9b03000

Guo, R., Zhao, B., Wang, Y., Wu, D., Wang, Y., Yu, Y., et al. (2018). Cichoric acid prevents free-fatty-acid-induced lipid metabolism disorders via regulating Bmal1 in HepG2 cells. *Journal of Agricultural and Food Chemistry, 66*(37), 9667–9678. https://doi.org/10.1021/acs.jafc.8b02147

Howitz, K. T., & Sinclair, D. A. (2008). Xenohormesis: Sensing the chemical cues of other species. *Cell, 133*(3), 387–391. https://doi.org/10.1016/j.cell.2008.04.019

Ibars, M., Aragonès, G., Ardid-Ruiz, A., Gibert-Ramos, A., Arola-Arnal, A., Suárez, M., et al. (2018). Seasonal consumption of polyphenol-rich fruits affects the hypothalamic leptin signaling system in a photoperiod-dependent mode. *Scientific Reports, 8*(1), 1–13. https://doi.org/10.1038/s41598-018-31855-y

Iglesias-Carres, L., Mas-Capdevila, A., Bravo, F. I., Arola, L., Muguerza, B., & Arola-Arnal, A. (2019). Exposure of Fischer 344 rats to distinct photoperiods influences the bioavailability of red grape polyphenols. *Journal of Photochemistry and Photobiology B: Biology, 199*, 111623. https://doi.org/10.1016/j.jphotobiol.2019.111623

Johnston, J. D. (2014). Physiological responses to food intake throughout the day. *Nutrition Research Reviews, 27*(1), 107–118. https://doi.org/10.1017/S0954422414000055

Johnston, J. D., Ordovás, J. M., Scheer, F. A., & Turek, F. W. (2016). Circadian rhythms, metabolism, and chrononutrition in rodents and humans. *Advances in Nutrition, 7*(2), 399–406. https://doi.org/10.3945/an.115.010777

Kalisz, S., Oszmiański, J., Kolniak-Ostek, J., Grobelna, A., Kieliszek, M., & Cendrowski, A. (2020). Effect of a variety of polyphenols compounds and antioxidant properties of rhubarb (Rheum rhabarbarum). *Lebensmittel-Wissenschaft und -Technologie, 118*, 108775. https://doi.org/10.1016/j.lwt.2019.108775

Kalsbeek, A., La Fleur, S., & Fliers, E. (2014). Circadian control of glucose metabolism. *Molecular Metabolism, 3*(4), 372–383. https://doi.org/10.1016/j.molmet.2014.03.002

Kecklund, G., & Axelsson, J. (2016). Health consequences of shift work and insufficient sleep. *BMJ, 355*, i5210. https://doi.org/10.1136/bmj.i5210

Kharwar, R. N., Sharma, V. K., Mishra, A., Kumar, J., Singh, D. K., Verma, S. K., et al. (2020). Harnessing the phytotherapeutic treasure troves of the ancient medicinal plant azadirachta indica (Neem) and associated endophytic microorganisms. In *Planta medica*. https://doi.org/10.1055/a-1107-9370

Korf, H.-W. (2018). Signaling pathways to and from the hypophysial pars tuberalis, an important center for the control of seasonal rhythms. *General and Comparative Endocrinology, 258*, 236–243. https://doi.org/10.1016/j.ygcen.2017.05.011

Leone, V., Gibbons, S. M., Martinez, K., Hutchison, A. L., Huang, E. Y., Cham, C. M., et al. (2015). Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host & Microbe, 17*(5), 681–689. https://doi.org/10.1016/j.chom.2015.03.006

Levi, F., & Schibler, U. (2007). Circadian rhythms: Mechanisms and therapeutic implications. *Annual Review of Pharmacology and Toxicology, 47*, 593–628. https://doi.org/10.1146/annurev.pharmtox.47.120505.105208

Lowrey, P. L., & Takahashi, J. S. (2004). Mammalian circadian biology: Elucidating genome-wide levels of temporal organization. *Annual Review of Genomics and Human Genetics, 5*, 407–441. https://doi.org/10.1146/annurev.genom.5.061903.175925

Luca, S. V., Macovei, I., Bujor, A., Miron, A., Skalicka-Woźniak, K., Aprotosoaie, A. C., et al. (2020). Bioactivity of dietary polyphenols: The role of metabolites. *Critical Reviews in Food Science and Nutrition, 60*(4), 626–659. https://doi.org/10.1080/10408398.2018.1546669

Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: Food sources and bioavailability. *American Journal of Clinical Nutrition, 79*(5), 727–774.

Man, A. W. C., Xia, N., Daiber, A., & Li, H. (2020). The roles of gut microbiota and circadian rhythm in the cardiovascular protective effects of polyphenols. *British Journal of Pharmacology, 177*(6), 1278–1293. https://doi.org/10.1111/bph.14850

Margalef, M., Pons, Z., Bravo, F. I., Muguerza, B., & Arola-Arnal, A. (2015). Plasma kinetics and microbial biotransformation of grape seed flavanols in rats. *Journal of Functional Foods, 12*, 478–488. https://doi.org/10.1016/j.jff.2014.12.007

Margalef, M., Pons, Z., Bravo, F. I., Muguerza, B., & Arola-Arnal, A. (2015). Tissue distribution of rat flavanol metabolites at different doses. *Journal of Nutritional Biochemistry, 26*(10), 987–995. https://doi.org/10.1016/j.jnutbio.2015.04.006

Margalef, M., Pons, Z., Iglesias-Carres, L., Bravo, F. I., Muguerza, B., & Arola-Arnal, A. (2017). Flavanol plasma bioavailability is affected by metabolic syndrome in rats. *Food Chemistry, 231*, 287–294. https://doi.org/10.1016/j.foodchem.2017.03.141

Margalef, M., Pons, Z., Iglesias-Carres, L., Quiñones, M., Bravo, F. I., Arola-Arnal, A., et al. (2017). Rat health status affects bioavailability, target tissue levels, and bioactivity of grape seed flavanols. *Molecular Nutrition & Food Research, 61*(2). https://doi.org/10.1002/mnfr.201600342

Mariné-Casadó, R., Domenech-Coca, C., del Bas, J. M., Bladé, C., Caimari, A., & Arola, L. (2019). Cherry consumption out of season alters lipid and glucose homeostasis in normoweight and cafeteria-fed obese Fischer 344 rats. *Journal of Nutritional Biochemistry, 63*, 72–86. https://doi.org/10.1016/j.jnutbio.2018.09.013

Mazrou, R. M. (2019). Moringa leaf extract application as a natural biostimulant improves the volatile oil content, radical scavenging activity and total phenolics of coriander Ragia M Mazrou. ~ *45* ~. *Journal of Medicinal Plants Studies, 7*(5), 45–51. http://www.plantsjournal.com.

McGinnis, G. R., & Young, M. E. (2016). Circadian regulation of metabolic homeostasis: Causes and consequences. *Nature and Science of Sleep, 8*, 163–180. https://doi.org/10.2147/NSS.S78946

Mi, Y., Qi, G., Fan, R., Ji, X., Liu, Z., & Liu, X. (2017). EGCG ameliorates diet-induced metabolic syndrome associating with the circadian clock. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1863*(6), 1575–1589. https://doi.org/10.1016/j.bbadis.2017.04.009

Miranda, J., Portillo, M. P., Madrid, J. A., Arias, N., Macarulla, M. T., & Garaulet, M. (2013). Effects of resveratrol on changes induced by high-fat feeding on clock genes in rats. *British Journal of Nutrition, 110*(8), 1421–1428. https://doi.org/10.1017/S0007114513000755

Mousavi, S. S., Karami, A., Haghighi, T. M., Alizadeh, S., & Maggi, F. (2021). Phytotoxic potential and phenolic profile of extracts from scrophularia striata. *Plants, 10*(1), 135. https://doi.org/10.3390/plants10010135

Murray, M., Dordevic, A., Ryan, L., & Bonham, M. (2019). A single-dose of a polyphenol-rich Fucus vesiculosus extract is insufficient to blunt the elevated postprandial blood glucose responses exhibited by healthy adults in the evening: A randomised crossover trial. *Antioxidants, 8*(2), 49. https://doi.org/10.3390/antiox8020049

Ohdo, S. (2003). Changes in toxicity and effectiveness with timing of drug administration: Implications for drug safety. *Drug Safety, 26*(14), 999–1010. https://doi.org/10.2165/00002018-200326140-00002

Oike, H., & Kobori, M. (2008). Resveratrol regulates circadian clock genes in Rat-1 fibroblast cells. *Bioscience Biotechnology and Biochemistry, 72*(11), 3038–3040. https://doi.org/10.1271/bbb.80426

Oldoni, T. L. C., Merlin, N., Bicas, T. C., Prasniewski, A., Carpes, S. T., Ascari, J., et al. (2021). Antihyperglycemic activity of crude extract and isolation of phenolic compounds with antioxidant activity from Moringa oleifera Lam. leaves grown in Southern Brazil. *Food Research International, 141*, 110082. https://doi.org/10.1016/j.foodres.2020.110082

Ożarowski, M., Karpiński, T. M., Szulc, M., Wielgus, K., Kujawski, R., Wolski, H., et al. (2021). Plant phenolics and extracts in animal models of preeclampsia and clinical trials—review of perspectives for novel therapies. *Pharmaceuticals, 14*, 269. https://doi.org/10.3390/ph14030269

Ozdal, T., Sela, D. A., Xiao, J., Boyacioglu, D., Chen, F., & Capanoglu, E. (2016). The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients, 8*(2), 78. https://doi.org/10.3390/nu8020078

Pan, Lai, C.-S., Wu, J.-C., & Ho, C.-T. (2013). Epigenetic and disease targets by polyphenols. *Current Pharmaceutical Design, 19*(34), 6156–6185. https://doi.org/10.2174/1381612811319340010

Pan, A., Schernhammer, E. S., Sun, Q., & Hu, F. B. (2011). Rotating night shift work and risk of type 2 diabetes: Two prospective cohort studies in women. *PLoS Medicine, 8*(12), Article e1001141. https://doi.org/10.1371/journal.pmed.1001141

Pérez-Jiménez, J., Neveu, V., Vos, F., & Scalbert, A. (2010). Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *European Journal of Clinical Nutrition, 64*, S112–S120. https://doi.org/10.1038/ejcn.2010.221

Qi, G., Wu, W., Mi, Y., Shi, R., Sun, K., Li, R., et al. (2018). Tea polyphenols direct Bmal1-driven ameliorating of the redox imbalance and mitochondrial dysfunction in hepatocytes. *Food and Chemical Toxicology, 122*, 181–193. https://doi.org/10.1016/j.fct.2018.10.031

Reppert, S. M., & Weaver, D. R. (2002). Coordination of circadian timing in mammals. *Nature, 418*(6901), 935–941. https://doi.org/10.1038/nature00965

Ribas-Latre, A., Baselga-Escudero, L., Casanova, E., Arola-Arnal, A., Salvadó, M. J., Arola, L., et al. (2015). Chronic consumption of dietary proanthocyanidins modulates peripheral clocks in healthy and obese rats. *The Journal of Nutritional Biochemistry, 26*(2), 112–119. https://doi.org/10.1016/j.jnutbio.2014.09.006

Ribas-Latre, A., Baselga-Escudero, L., Casanova, E., Arola-Arnal, A., Salvadó, M. J., Bladé, C., et al. (2015). Dietary proanthocyanidins modulate BMAL1 acetylation, Nampt expression and NAD levels in rat liver. *Scientific Reports, 5*(1), 1–13. https://doi.org/10.1038/srep10954

Ribas-Latre, A., Del Bas, J. M., Baselga-Escudero, L., Casanova, E., Arola-Arnal, A., Salvadó, M.-J., et al. (2015). Dietary proanthocyanidins modulate melatonin levels in plasma and the expression pattern of clock genes in the hypothalamus of rats. *Molecular Nutrition & Food Research, 59*(5), 865–878. https://doi.org/10.1002/mnfr.201400571

Ribas-Latre, A., Del Bas, J. M., Baselga-Escudero, L., Casanova, E., Arola-Arnal, A., Salvadó, M. J., et al. (2015). Dietary proanthocyanidins modulate the rhythm of BMAL1 expression and induce RORα transactivation in HepG2 cells. *Journal of Functional Foods, 13*, 336–344. https://doi.org/10.1016/j.jff.2015.01.017

Sahar, S., & Sassone-Corsi, P. (2012). Regulation of metabolism: The circadian clock dictates the time. *Trends in Endocrinology and Metabolism, 23*(1), 1–8. https://doi.org/10.1016/j.tem.2011.10.005

Shahidi, F., & Yeo, J. D. (2018). Bioactivities of phenolics by focusing on suppression of chronic diseases: A review. *International Journal of Molecular Sciences, 19*(6), 1573. https://doi.org/10.3390/ijms19061573

Sharma, A., Shahzad, B., Rehman, A., Bhardwaj, R., Landi, M., & Zheng, B. (2019). Response of phenylpropanoid pathway and the role of polyphenols in plants under abiotic stress. *Molecules, 24*(13), 2452. https://doi.org/10.3390/molecules24132452

Shinozaki, A., Misawa, K., Ikeda, Y., Haraguchi, A., Kamagata, M., Tahara, Y., et al. (2017). Potent effects of flavonoid nobiletin on amplitude, period, and phase of the circadian clock rhythm in PER2::LUCIFERASE mouse embryonic fibroblasts. *PloS One, 12*(2), Article e0170904. https://doi.org/10.1371/journal.pone.0170904

Soengas, P., Cartea, M. E., Velasco, P., & Francisco, M. (2018). Endogenous circadian rhythms in polyphenolic composition induce changes in antioxidant properties in Brassica cultivars. *Journal of Agricultural and Food Chemistry, 66*(24), 5984–5991. https://doi.org/10.1021/acs.jafc.8b01732

Sun, L., Wang, Y., Song, Y., Cheng, X. R., Xia, S., Rahman, M. R. T., et al. (2015). Resveratrol restores the circadian rhythmic disorder of lipid metabolism induced by high-fat diet in mice. *Biochemical and Biophysical Research Communications, 458*(1), 86–91. https://doi.org/10.1016/j.bbrc.2015.01.072

Takahashi, M., Ozaki, M., Miyashita, M., Fukazawa, M., Nakaoka, T., Wakisaka, T., et al. (2019). Effects of timing of acute catechin-rich green tea ingestion on postprandial glucose metabolism in healthy men. *Journal of Nutritional Biochemistry, 73*, 108221. https://doi.org/10.1016/j.jnutbio.2019.108221

Tan, X., Li, L., Wang, J., Zhao, B., Pan, J., Wang, L., et al. (2019). Resveratrol prevents acrylamide-induced mitochondrial dysfunction and inflammatory responses via targeting circadian regulator Bmal1 and Cry1 in hepatocytes. *Journal of Agricultural and Food Chemistry, 67*(31), 8510–8519. https://doi.org/10.1021/acs.jafc.9b03368

Tsao, R. (2010). Chemistry and biochemistry of dietary polyphenols. *Nutrients, 2*(12), 1231–1246. https://doi.org/10.3390/nu2121231

Van Duynhoven, J., Vaughan, E. E., Jacobs, D. M., Kemperman, R. A., Van Velzen, E. J. J., Gross, G., et al. (2011). Metabolic fate of polyphenols in the human superorganism. *Proceedings of the National Academy of Sciences of the United States of America, 108*(SUPPL. 1), 4531–4538. https://doi.org/10.1073/pnas.1000098107

Voigt, R. M., Forsyth, C. B., Green, S. J., Engen, P. A., & Keshavarzian, A. (2016). Circadian rhythm and the gut microbiome. In *International review of neurobiology, 131* pp. 193–205). Academic Press Inc. https://doi.org/10.1016/bs.irn.2016.07.002.

Voigt, R. M., Summa, K. C., Forsyth, C. B., Green, S. J., Engen, P., Naqib, A., et al. (2016). The circadian clock mutation promotes intestinal dysbiosis. *Alcoholism: Clinical and Experimental Research, 40*(2), 335–347. https://doi.org/10.1111/acer.12943

Young, M. W., & Kay, S. A. (2001). Time zones: A comparative genetics of circadian clocks. *Nature Reviews Genetics, 2*(9), 702–715. https://doi.org/10.1038/35088576

Zhou, B., Zhang, Y., Zhang, F., Xia, Y., Liu, J., Huang, R., et al. (2014). CLOCK/BMAL1 regulates circadian change of mouse hepatic insulin sensitivity by SIRT1. *Hepatology, 59*(6), 2196–2206. https://doi.org/10.1002/hep.26992

Ziaullah, & Rupasinghe, H. P. V. (2015). Application of NMR spectroscopy in plant polyphenols associated with human health. In *Applications of NMR spectroscopy, 2* pp. 3–92). Elsevier Inc. https://doi.org/10.1016/B978-1-60805-999-7.50001-X.

Zimmet, P., Alberti, K. G. M. M., Stern, N., Bilu, C., El-Osta, A., Einat, H., et al. (2019). The circadian syndrome: Is the metabolic syndrome and much more! *Journal of Internal Medicine, 286*, 181–191. https://doi.org/10.1111/joim.12924