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Interplay between (poly)phenols, gut microbiota, and biological rhythms: outlook for a new paradigm in brain health

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ABSTRACT

Dietary (poly)phenols, bioactive compounds abundantly found in plant-based foods, undergo extensive metabolism by the host and its gut microbiota, producing metabolites that influence systemic and brain health. Despite their low bioavailability, (poly)phenols have been consistently associated with neuroprotective benefits, such as reducing neuroinflammation and enhancing gut-brain communication. Additionally, circadian rhythms can influence (poly)phenol bioactivity, while these compounds, in turn, modulate biological rhythms. The gut microbiota's diurnal oscillations affect (poly)phenol metabolism and modulate (poly)phenols' effects by producing bioactive metabolites, adding complexity to their health impact. Understanding these mechanisms can aid in designing functional foods and precision nutrition strategies to enhance neuroprotection. However, critical questions remain unanswered. This review explores the interplay between (poly)phenols, circadian rhythms, and gut microbiota, highlighting their collective role in brain health. The influence of individual gut microbiota profiles, polyphenol-related metabolotypes, and circadian synchrony on (poly)phenol metabolism and neuroprotection is not fully understood. Likewise, the timing of (poly)phenol consumption and its interaction with rhythmic microbial processes require further exploration. Addressing these gaps could lead to targeted dietary interventions. Future research should prioritize human trials and multi-omics approaches to unravel these complex relationships, advancing precision health strategies that foster cognitive resilience and reduce neurodegenerative disease risk.

KEYWORDS

Circadian rhythms; interindividual variability; neuroprotection; metabolotype; phenolic compounds; seasonal rhythms

1. (Poly)phenols and health: an increasingly complex puzzle

All polyphenols are phenolic compounds, but not all phenolic compounds are polyphenols. Therefore, the term “phenolic compounds” can be abbreviated as “(poly)phenols” to reflect this distinction. (Poly)phenols are non-nutrient molecules found in plant-based foods. We ingest (poly)phenols with hundreds of different molecular structures through our diet by consuming plant foods, including fruits, vegetables, cereals, and derivatives such as tea, coffee, virgin olive oil, and red wine. The focus on (poly)phenols and health has evolved historically from potentially harmful xenobiotics with mutagenic and anti-nutritional properties to molecules claimed to have preventive effects against chronic diseases (obesity, cardiovascular diseases, diabetes, Alzheimer's, Parkinson's, and others) through a multitude of mechanisms (Davies 1979; Williamson, Kay, and Crozier 2018). These mechanisms include the regulation of lipid metabolism, platelet aggregation, inflammation, cell proliferation and

apoptosis, redox status, endothelial function, and autophagy/mitophagy, among others (García-Villalba et al. 2023; Granados-Soto 2003; Larrosa et al. 2010; Martin, Goya, and Ramos 2016; Monfoulet et al. 2021; Sanches-Silva et al. 2020). A meta-analysis (Ma and Chen 2020) suggested that an approximate 500 mg/day intake impacts the human gut microbiota. However, it remains inconclusive as to which types of (poly)phenols, the optimal duration of intake, and the specific health outcomes according to physiological status. Thus, given the high structural heterogeneity of (poly)phenols, we are still far from precisely determining which types should be consumed, for how long, and under what conditions and physiological contexts. Therefore, it is necessary to understand the role of all the pieces in this complex puzzle formed by (poly)phenols and their effects on health.

Absorption, disposition, metabolism, and excretion studies showed that (poly)phenols are poorly bioavailable, alongside an enormous structural diversity found in the Plant Kingdom, with nearly 10,000 molecules possessing a

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phenolic structure (i.e., one or more hydroxyl groups on aromatic rings) and several hundred present in dietary plant foods (Manach et al. 2004; Williamson 2025). Only a tiny fraction of the ingested (poly)phenols circulates in the bloodstream, making direct interaction with systemic cells unlikely. Instead, (poly)phenols are metabolized in the intestine and liver by phase II enzymes, resulting in conjugated derivatives, which circulate in the blood, reach systemic tissues, and are eventually excreted in the urine. However, most consumed (poly)phenols reach the colon, where they undergo extensive metabolism by the gut microbiota. The microbial-derived metabolites produced are more bioavailable than their (poly)phenolic precursors but rarely circulate as free forms. Instead, they also undergo phase II conjugations, producing microbial-derived conjugated metabolites that circulate, reach systemic tissues, and are excreted in the urine. Finally, a significant portion of the ingested (poly)phenols, especially those with higher molecular mass like oligomers and polymers and other non-absorbed microbial-derived metabolites, are excreted in feces. Both ingested (poly)phenols and their derived metabolites undergo active enterohepatic circulation, ultimately aiming to maximize the metabolism and excretion of (poly)phenols (Cortés-Martín et al. 2020). Since (poly)phenols are non-nutritional xenobiotics with high reactivity, this extensive metabolism represents the evolutionary response to their potential threat to the host and its microbiota. Consequently, the resulting biological effects are mostly a consequence of the host and its microbiota's adaptation through differential (poly)phenol metabolism (Espín et al. 2024).

Thus, this apparent paradox (systemic effects but low bioavailability) implies that we are still far from establishing a universal cause-and-effect relationship between (poly)phenol consumption and health effects, and we are even further from unequivocally knowing what actor(s) is ultimately responsible for the biological effects following their consumption (Iglesias-Aguirre et al. 2021; Li and Van de Wiele 2023). Therefore, the effects could be exerted by the ingested polyphenols and (or) phase II conjugates and (or) microbial-derived metabolites and (or) their phase II conjugates. Moreover, it remains unclear which context predominates, i.e., whether the direct effects occur within the gastrointestinal tract, projecting systemically through signaling cascades, or if the systemic effect primarily arises from interactions with biological targets, whether it is the consumed (poly)phenol, its phase II metabolite, or the resulting microbial metabolites. Additionally, the gut microbial ecology of each individual (including gut microbiota metabolotypes), associated with (poly)phenol metabolism, might directly contribute to these health effects beyond the type and abundance of microbial metabolites produced (Cortés-Martín et al. 2020; Espín et al. 2024; Frankenfeld 2017; García-Villalba et al. 2022; Iglesias-Aguirre et al. 2021, 2022; Iglesias-Aguirre, Romo-Vaquero et al. 2023).

At this crossroads, the well-known two-way interaction between (poly)phenols and the gut microbiota has been recognized as a crucial factor in the health effects of (poly)phenols. On the one hand, the gut microbiota extensively

metabolizes dietary (poly)phenols into simpler metabolites that often have different bioavailability and biological activity compared to their precursors (Cortés-Martín et al. 2020; González-Sarriás et al. 2022; Iglesias-Aguirre et al. 2021). Many gut bacteria species have been identified in (poly)phenol transformations (Braune and Blaut 2016; Iglesias-Aguirre, García-Villalba, et al. 2023; Iglesias-Aguirre, González-Sarriás, et al. 2023; Jin and Hattori 2012; Selma et al. 2014, 2017; Xiong et al. 2023). However, significant interindividual variability exists in the production of (poly)phenol-derived metabolites due to each person's unique gut microbiota (Cortés-Martín et al. 2020; Espín, González-Sarriás, and Tomás-Barberán 2017; García-Villalba et al. 2022; Iglesias-Aguirre et al. 2021; Iglesias-Aguirre, Romo-Vaquero, et al. 2023; Kerimi et al. 2020; Romo-Vaquero et al. 2019; Zheng et al. 2019).

On the other hand, exposure to (poly)phenols can alter the composition and functionality of the gut microbiota. This alteration is influenced by the specific class of (poly)phenol, the length of exposure, and the individual's existing gut microbiota composition and functionality. In humans, this often leads to increased beneficial gut microbial groups such as lactobacilli, bifidobacteria, and butyrate-producers like *Roseburia* and *Faecalibacterium prausnitzii*. Conversely, it leads to a decrease in pro-inflammatory microbial groups (*Parvimonas*, *Methanobrevibacter*, among others) and opportunistic pathogens, mainly from the *Enterobacteriaceae* family, many of which produce lipopolysaccharides (LPS) involved in metabolic endotoxemia (*Escherichia-Shigella*, *Enterobacter*, *Citrobacter*, and others) (Cortés-Martín et al. 2020; Iglesias-Aguirre et al. 2021).

In recent years, the importance of interindividual variability in the context of (poly)phenols and health has become increasingly acknowledged. Not everyone responds similarly to (poly)phenols consumption (González-Sarriás et al. 2017). This variability is mainly associated with intrinsic factors such as a person's (epi)genetics, age, sex, and, as mentioned, the composition and functionality of their gut microbiota. Additionally, extrinsic factors can influence (poly)phenol absorption and interaction with the gut microbiota, including the food matrix, processing methods, and cooking techniques. Lifestyle factors that impact the microbiota's composition and functionality, such as physical activity, alcohol consumption, smoking, and medication use, also play a crucial role in the metabolism and activity of ingested (poly)phenols (Cortés-Martín et al. 2018; Cortés-Martín et al. 2020; Espín, González-Sarriás, and Tomás-Barberán 2017; Iglesias-Aguirre et al. 2021; Tomás-Barberán and Espín 2019).

To further complete the puzzle, mounting evidence emphasizes the role of biological rhythms as a relevant factor affecting the bioavailability and biological activity of (poly)phenols. It has been observed in animal models that the effectiveness of certain (poly)phenols can vary depending on the timing of administration (Escobar-Martínez et al. 2022; Huang, Lu, and Ho 2021; Navarro-Masip et al. 2023; Spaleniak and Cuendet 2023; Torres-Fuentes et al. 2022), and in turn, phenolic compounds would be able to influence biological rhythms (Ávila-Román et al. 2021; Huang, Lu, and

Ho 2021; Soliz-Rueda et al. 2022; Spaleniak and Cuendet 2023). This chronomodulation may depend on the physiological status (Soliz-Rueda et al. 2023) and contribute to the indirect mechanisms (regulation of peripheral clock miRNA, lipid metabolism, among others) through which polyphenols exert their effects (Colom-Pellicer et al. 2022; Manocchione et al. 2022; Navarro-Masip et al. 2023; Torres-Fuentes et al. 2022). In tandem, there is a growing appreciation of the interactions between the gut microbiota and circadian systems and how this may shape stress, metabolic and immune function in the context of brain disorders (Gheorghe et al. 2024; Soliz-Rueda et al. 2025; Tofani, Clarke, and Cryan 2025; Tofani et al. 2025).

As discussed, if it is unclear who the final actor responsible for the effects of (poly)phenols consumption is, this question becomes particularly relevant regarding their potential neuroprotective activity. Considering their low bioavailability, it is still debated whether the effects of (poly)phenols on brain health are directly mediated by their derived metabolites, possibly from the gut microbiota, which can cross the blood-brain barrier, and (or) if it is a “billiard-type” effect, in which the effect is exerted by a molecule that is not directly derived from the precursor (poly)phenol (e.g., nitric oxide production, activation of the Nrf2 pathway, among others), or which of these scenarios occurs depending on the ingested (poly)phenol (García-Villalba et al. 2023; Iglesias-Aguirre et al. 2021). In this regard, recent studies have described the detection of gut microbiota metabolites in brain parenchyma, such as urolithin A (Uro-A), derived from ellagic acid metabolism, preventing age-associated neuroinflammation through the induction of mitophagy (Jiménez-Loygorri et al. 2024). It has also been described the passage through the blood-brain barrier and the anti-(neuro)inflammatory activity of other (poly)phenols and derived metabolites, such as flavanols, simple phenolic acids, and related low-molecular-weight metabolites, commonly produced in the metabolism of the vast majority of (poly)phenols by the gut microbiota (Carecho, Carregosa, and dos Santos 2021; Margalef et al. 2016). Notably, the sex-dependent metabolic profiling of flavanol metabolites in the brain has been previously reported, which adds another layer of complexity to the puzzle (Margalef et al. 2016).

Understanding the relationship between (poly)phenols and health becomes increasingly complex as new variables are identified. In this context, we aim to offer a perspective on the interaction between gut microbiota, (poly)phenols, and circadian rhythms, focusing on brain health. Thus, with this objective in mind, we have approached the topic step by step, starting with briefly discussing well-known binomial interactions (i.e., polyphenols-gut microbiota and polyphenols-brain health, which are not the focus of this review) to advancing into well-known but still expanding trinomial interactions, such as polyphenols-gut microbiota-brain health and polyphenols-gut microbiota-circadian rhythms, culminating in a holistic approach that considers all the factors together: polyphenols, circadian rhythms, gut microbiota, and brain health.

2. (Poly)phenols, biological rhythms, and brain health

Most organisms, including animals, plants, fungi, and bacteria, undergo physiological oscillations to anticipate changes in their environmental conditions. The rhythmicity of these oscillations is mainly measured in periods of approximately 24h, known as circadian rhythms, which are related to the Earth's rotation around its axis, or as seasonal or circannual rhythms, resulting from the movement of the Earth around the sun. Accordingly, environmental cues such as light, temperature, stress, or food availability and timing, also known as “zeitgebers” (German for “time giver”), lead to circadian and circannual oscillations generated endogenously by a network of central and peripheral clocks that regulate endocrine, cardiovascular, immune, and neurological functions (Patke, Young, and Axelrod 2020). Hence, biological rhythms affect relevant processes of the organism, including brain function. Thus, the circadian clock regulates neuroinflammation, neurodegeneration, neurogenesis, and microglia functions (Jiao, Kalsbeek, and Yi 2024; Malik et al. 2015; Wang and Li 2021; Xu, Wang, and Chen 2023). These rhythms can also influence the effects of bioactive compounds such as (poly)phenols, which have emerged as an important factor to consider when investigating their bioactivities. Thus, biological rhythms have been shown to significantly influence the bioavailability of (poly)phenols metabolites, which potentially will be translated into different health effects (Arreaza-Gil et al. 2023; Escobar-Martínez et al. 2022). At the same time, (poly)phenols can exert some of their effects by modulating biological rhythms through different mechanisms, including central and peripheral clock regulation (Ávila-Román et al. 2021).

In the context of brain health, epidemiological evidence suggests that higher intake of (poly)phenol-rich foods may be associated with better cognitive function and a reduced risk of neurodegenerative diseases (Hunt, Pontifex, and Vauzour 2024). For example, preclinical and clinical studies have shown that (poly)phenols intake prevents or ameliorates cognitive decline (Caruso et al. 2022), depression (Gamage et al. 2023), stress (Sakakibara and Shimoï 2020) or anxiety (Pizarro Meléndez et al. 2024) among others. These effects have been linked to the modulation of neuroinflammation, neurogenesis, neuronal signaling, and gut microbiota composition. However, the underlying mechanisms remain poorly understood. In this regard, the above-mentioned bidirectional relationship between biological rhythms and phenolic compounds may explain some of the observed effects (Ávila-Román et al. 2021). Indeed, disruption of biological rhythms has been associated with an increased risk of brain disorders. Thus, shift workers are more susceptible to developing psychiatric disorders such as depression (Logan and McClung 2019), and circadian alterations have been linked to neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), or Huntington's disease, as well as to frontotemporal dementia (Nassan and Videnovic 2022). Moreover, rodent and brain neuron studies have demonstrated that circadian rhythms regulate amyloid- β dynamics in the brain (Xu and Lu 2019).

In the case of PD and AD, their relationship with biological rhythms seems to be bidirectional. Thus, impaired sleep and circadian homeostasis have been observed in these patients, and disrupted circadian rhythms have been linked to a higher risk of developing these diseases (Xu and Lu 2019). Therefore, modulating biological rhythms by bioactive compounds such as (poly)phenols may be relevant in these brain-related disorders. In fact, the modulation of circadian rhythms by natural products has been proposed as a new target against different pathologies, including those related to brain function (Xin et al. 2024).

Although minimal evidence exists, some (poly)phenols-mediated effects in brain-related pathways have been linked to biological rhythms. For example, intake of 2 g/L tea (poly)phenols led to neuroprotective effects and ameliorated memory impairments caused by circadian desynchrony in C57BL/6J mice kept in constant darkness (Qi, Mi, Liu, et al. 2017; Qi, Mi, Wang, et al. 2017). The authors related these effects to recovering the daily oscillations of circadian clock gene transcription and protein expression in the hypothalamus. In addition, administration of 0.1% (w/w) of tea (poly)phenols for 4 wks led to an increased number of hypothalamic astrocytes and oligodendrocytes and adjusted expression of relevant genes in the molecular clock such as casein kinase 1 delta (*Csnk1d*), circadian locomotor output cycles kaput (*Clock*), period 3 (*Per3*), cryptochrome 2 (*Cry2*), and basic helix-loop-helix family member e41 (*Bhlhe41*) caused by circadian disruption in C57BL/6J male mice (Zhang et al. 2022). Consumption of other phenolic compounds, such as proanthocyanidins from a grape seed extract (250 mg/kg), have been shown to modulate melatonin levels in plasma and the expression pattern of clock genes (brain and muscle Arnt-like protein-1 (*Bmal1*) and nicotinamide phosphoribosyltransferase (*Nampt*) in the hypothalamus of male Wistar rats (Ribas-Latre et al. 2015). These effects were observed when proanthocyanidins were administered at ZT3 (3 h after lights were turned on), while they were lost when administered at ZT12 (when light was turned off). Hence, the effects of proanthocyanidins might depend on the administration time.

Moreover, administering flavonoids from a sweet tea tree (*Cyclocarya paliurus*; CPF) (200 mg/kg) significantly regulated the expression of genes associated with circadian rhythm, myelination, and neurodegenerative diseases in a circadian rhythm disorder mouse model (Sun et al. 2022). Furthermore, the intake of cocoa (2%) ameliorated disrupted circadian rhythms in locomotor activity and sleep-wake cycles in male C3H/HeN mice with chronic sleep disorders caused by 30 days of exposure to psychophysiological stress (Oishi et al. 2020). In addition, supplementation with 200 mg/kg/d of resveratrol in the non-human primate grey mouse lemur for 3 wks led to a significantly increased proportion of active wake time and a significant reduction of both paradoxical and slow-wave sleep. These changes mainly occurred during the resting phase of the sleep-wake cycle. Hence, the authors concluded that resveratrol might be of significant interest in studying sleep perturbations associated with aging and neuropathology (Pifferi et al. 2012). In another study, oral administration of a dietary flavonoid

(fisetin at 50 mg/kg) to hyperammonemic rats improved circadian locomotor activity, redox balance in the brain, and astrocytic markers (Subramanian et al. 2015). Authors associated these effects with antioxidant, anti-inflammatory, cytoprotective, neuroprotective, and neurotrophic properties of fisetin. Moreover, in a recent review, the protective effects of chocolate intake against brain function alterations caused by the disruption of circadian rhythms in humans were linked to its content of flavanols, especially epicatechin, and their capacity to regulate circadian rhythms (Garbarino, Garbarino, and Lanteri 2022). The authors highlighted that these beneficial effects were obtained when chocolate was consumed in modest amounts and during the first hours of the active phase to avoid weight gain problems. Recently, it has also been shown that administration of Japanese quince fruit juice at different doses (2.5 and 10 ml/kg), which is rich in (poly)phenols, improved social interaction and decreased anxiety- and depression-like behavior in male Wistar rats subjected to impaired circadian rhythms (Borisova-Nenova, Eftimov, and Valcheva-Kuzmanova 2023).

There are few studies on the effects of (poly)phenols on brain-related pathways and their relationship with seasonal rhythms. For example, the consumption of 100 mg/kg of lyophilized red grapes or cherries affected the hypothalamic leptin signaling system in a photoperiod-dependent manner in both non-obese and obese Fischer 344 rats, with a more significant effect under short photoperiod conditions (6 h light/day) (Ibars et al. 2018). In another study, administration of 100 mg/kg of lyophilized sweet cherries to healthy Fisher 344 rats upregulated hippocampal brain-derived neurotrophic factor (*Bdnf*), nuclear factor erythroid-derived 2-like (*Nrf2*), neuronal differentiation 1 (*NeuroD*), and glutathione peroxidase 1 (*Gpx1*) gene expression levels in healthy Fisher 344 rats compared with control rats (Manocchio et al. 2024). Interestingly, these antioxidant and neuroprotective properties were observed only when rats consumed cherries housed under a long photoperiod (18 h light/day), suggesting that these effects were regulated by photoperiod. In addition, when sweet cherries from other origins and with other phenolic hallmarks were administered to the animals, no effects were observed, indicating that the composition of sweet cherries was also essential.

Evidence from human studies regarding the beneficial effects of (poly)phenols on brain health and its link to the modulation of biological rhythms is scant. The available few studies are focused on the associations between (poly)phenols consumption and sleep quality, which is of interest as this process is closely related to circadian rhythm, and its alterations have been linked to impairments in brain function (Hibi 2023). For example, in an epidemiologic study, adult participants from southern Italy who consumed higher intakes of flavonoids, such as flavanones and flavones, as well as phenolic acids and lignans, had higher sleep quality. Interestingly, this association was lost in overweight/obese individuals (Godos et al. 2020). In another study on women from the UK, consuming (poly)phenol-rich foods such as vegetables and fruits was associated with shorter sleep (Noorwali, Hardie, and Cade 2018). Moreover, a randomized, placebo-controlled, double-blinded cross-over trial,

consuming 600 mg of chlorogenic acid for 5 days, showed decreased sleep latency and enhanced parasympathetic activity assessed from heart-rate variability during sleep (Park et al. 2017). In a recent review summarizing the current state of the art on the potential of (poly)phenols to modulate sleep, three out of four human observational studies found a positive correlation between consuming (poly)phenols and sleep parameters.

Among clinical intervention studies, a beneficial effect of (poly)phenols intake was found on various sleep parameters in eight out of 12 studies. However, discrepancies related to the relationship between fruit, vegetable, and total polyphenol intake and sleep duration were found (Pérez-Jiménez et al. 2023). In a study with adults with sleep complaints but not sleep disorders, the intake of a (poly)phenol extract from spearmint/green tea (dose not specified) for 30 days led to improvements in nighttime and day-time sleep-related variables, as well as cognitive function (Grandner et al. 2019). However, more human studies, especially randomized controlled trials, need to confirm (poly)phenol effects in sleep disorders and their relationship with biological rhythms modulation and brain function.

3. Gut microbiota, biological rhythms, and brain health

Research has revealed that gut microbiota undergoes diurnal oscillations, which have significant implications for human health, impacting host metabolism, immunity, and brain health (Li et al. 2024; Schmid et al. 2023). These rhythmic changes in microbial composition align with the body's circadian rhythms and feeding diurnal patterns and can influence various physiological processes. For example, approximately 15% of bacterial operational taxonomic units (OTUs) and up to 60% of the bacterial community, including taxa such as Clostridiales, Lactobacillales, and Bacteroidales, have been shown to exhibit diurnal fluctuations in mice that correlated with oscillations in its functional capacity (Thaiss et al. 2014). Hence, there was an increase in genes related to energy metabolism, DNA repair, and cell growth during the active phase, while a higher abundance of pathways involved in detoxification, motility, and environmental sensing was observed during the resting phase in mice (Thaiss et al. 2014). Moreover, several gut microbiota-derived bioactive metabolites also fluctuate throughout the day. Thus, SCFAs have been shown to exhibit diurnal oscillations and synchronize peripheral clocks in mice (Segers et al. 2019; Tahara et al. 2018). Also, gastrointestinal tryptophan metabolism has been reported to exhibit diurnal rhythms that depend on the gut microbiota's diurnal rhythmicity in mice (Gheorghe et al. 2024). Fluctuation of bile acids, which are metabolized by gut microbiota, has also been observed during the day, with increased levels during the active phase in mice (Yang and Zhang 2020). Moreover, another study in C57BL/6J mice linked intestinal clock-controlled bacteria to microbial-derived products, particularly branched-chain fatty acids and secondary bile acids (Heddes et al. 2022). In addition, the gut microbiota-derived metabolite trimethylamine *N*-oxide (TMAO) has been shown

to regulate circadian rhythms in C57BL/6J mice (Schugar et al. 2022) and has been associated with the chronotype score in humans (Barrea et al. 2021). Indeed, it was recently hypothesized that the gut microbiota might act as non-photic “zeitgebers” to entrain the host's circadian clock and metabolism (Choi, Rao, and Chang 2021). Moreover, epigenetic mechanisms have been proposed to be disturbed without microbial oscillation. Indeed, microbiota ablation reduced the rhythmic expression of histone deacetylase 3 (HDAC3) in mouse epithelial cells of the small intestine, which was linked to intestinal metabolic gene expression and lipid metabolism (Kuang et al. 2019).

Interestingly, disruption of circadian rhythms has been shown to alter gut microbiota, contributing to the development of metabolic pathologies such as type 2 diabetes (T2D) in humans (Moreno-Cortés et al. 2024; Reitmeier et al. 2020). Ablation of the core clock gene *Bmal1* in mice on a genetic C57BL/6J background was shown to disrupt the rhythmicity of the gut microbiota, highlighting that a functional intestinal clock is crucial for regulating the circadian dynamics of both gut microbiota composition and function (Heddes et al. 2022). In addition, unhealthy dietary habits and changes in the timing of food intake may disrupt the rhythmicity of the gut microbiota, which can act synergistically with a dysregulated circadian clock to increase metabolic risk (Soliz-Rueda et al. 2025). Indeed, a recent systemic review of preclinical data showed that disruption of circadian rhythms by a Western diet decreases the diversity of gut microbiota and promotes the growth of harmful bacterial groups such as *Clostridaceae*, *Enterococcus*, *Parasutterella*, and *Proteobacteria*, increasing the risk of metabolic diseases (Moreira Gobis, Goulart de Souza-Silva, and de Almeida Paula 2024). This is reinforced by the finding that gut microbiota diurnal oscillations were disrupted in type 2 diabetic (db/db) mice and could be correlated with changes in diurnal patterns of metabolic pathways (Beli et al. 2019). Future research should explore the relationship between microbiota oscillations and circadian regulation of metabolic health and whether microbiota-mediated effects and circadian influences converge on metabolic health through the central regulation of homeostatic eating behaviors (Soliz-Rueda et al. 2025).

Noteworthy, the gut microbiota is now also firmly established as a crucial factor in gut-brain-axis signaling and an essential communicator for maintaining brain health (Berding, Long-Smith, et al. 2021; Cryan et al. 2019). Indeed, the gut microbiota can impact brain and behavior (Cryan and Dinan 2012) and has an evidence base for its involvement in stress and stress-related disorders (Berding et al. 2023), including anxiety and depression (Simpson et al. 2021), and neurodegenerative diseases (Loh et al. 2024), such as AD and PD (Solch et al. 2022) and even neuropsychiatric disorders (Hashimoto 2023). This has led to an increasing focus on dietary interventions with the potential to improve these conditions via the modulation of the gut microbiota. For example, a recent randomized trial using a psychobiotic diet, defined as high in prebiotic and fermented foods, demonstrated reduced perceived stress, the effect of which was correlated to how much the microbiota changed

from baseline (microbial volatility) (Berding et al. 2023). Another recent systematic review and meta-analysis of observational studies and randomized controlled trials demonstrated a potential benefit for higher fiber intake in depression and anxiety. However, they concluded that more evidence is needed to definitively promote fiber supplementation as a strategy for enhancing outcomes related to depression and anxiety (Aslam et al. 2023). Furthermore, prebiotics are suggested to support cognitive resilience in the face of lifestyle and age-related challenges (Dalile et al. 2025). For example, supplementation with 12.5 g of the dietary fiber polydextrose in healthy female participants in an exploratory randomized, placebo-controlled crossover study demonstrated a modest improvement in sustained attention performance, which correlated to a significant increase in the abundance of *Ruminiclostridium* in another recent randomized clinical trial (Berding, Long-Smith, et al. 2021).

While these studies point to the potential for microbiota-targeted approaches to enhance brain function, the mechanisms are still not fully elucidated (Schellekens et al. 2023). Mainly, preclinical studies have demonstrated the potential for gut microbiota and its metabolites to interact with the gut-brain axis via the immune system, the modulation of tryptophan metabolism, the vagus nerve, and the enteric nervous system (Cryan et al. 2019). This communication involves microbial metabolites such as conjugated bile acids, branched-chain amino acids (BCAAs), peptidoglycans, and SCFAs (O'Riordan et al. 2022). Especially prolific have been the investigations into the effects of SCFAs, which can enter the systemic circulation and pass the blood-brain barrier, and hence have demonstrated a wide range of beneficial effects on the central nervous system, including a potential role in brain inflammation and mood disorders (O'Riordan et al. 2022).

While these findings likely have implications for brain function, only a few recent studies have demonstrated findings highlighting the interaction of gut microbiota, the host's circadian clock, and brain function, with limited to no translational evidence. For example, a recent role of the gut microbiota as a chronoregulator of hypothalamic–pituitary–adrenal (HPA) axis rhythmic function was demonstrated (Tofani, Clarke, and Cryan 2025). This study demonstrated a dysregulated master circadian pacemaker and altered glucocorticoid rhythmicity coupled with altered transcriptome and metabolome profiles in the hippocampus and amygdala of mice with depleted gut microbiota. Overall, this resulted in HPA axis over-activation and impaired stress-related behaviors. This is the first evidence highlighting the role of the gut microbiota in the circadian regulation of stress responses, which is essential for adapting to psychological stress throughout the day.

Thus, recent evidence demonstrates that the gut microbiota experiences diurnal oscillations that align with the host's circadian rhythms, which can impact the brain and behavior. Disruptions in these rhythms due to microbiota perturbations following changes in eating patterns or diet, stress, or circadian misalignment can exacerbate cognitive decline, neurodegenerative conditions, and mental health issues.

Thus, maintaining a balanced microbiota aligned with the body's natural circadian rhythms is crucial for optimal brain health and cognitive function.

4. Joining the pieces: (poly)phenols, biological rhythms, gut microbiota, and brain health

Both (poly)phenols and gut microbiota have been shown to modulate brain function, and biological rhythms are emerging as a potentially important component that could mediate these effects. However, the joint interaction of all these factors is not yet well understood.

As mentioned above, phenolic compounds have low bio-availability and above 90% reach the colon, where they undergo extensive metabolism by gut bacteria via deglycosylation, reduction, ring cleavage, dehydroxylation, and demethylation reactions, among others. This process can produce a great variety of metabolites, which are absorbed and usually conjugated by phase-II host's enzymes and then distributed to different tissues, including the brain in some cases, exerting different beneficial effects (Cortés-Martín et al. 2020; Espín, González-Sarriás, and Tomás-Barberán 2017; Espín et al. 2024; García-Villalba et al. 2023; Iglesias-Aguirre et al. 2021). Since changes in gut bacteria are induced by internal and external factors, biological rhythms may affect the gut microbiota and produce different (poly)phenols-derived metabolites impacting health effects, including those related to brain function (García-Villalba et al. 2023; Hunt, Pontifex, and Vauzour 2024). Notably, the prebiotic effect of (poly)phenols can also be affected by biological rhythms since, as already mentioned, bioactivities of phenolic compounds and gut microbiota composition are modulated by this factor (Ávila-Román et al. 2021). In addition, the effects of the bidirectional relationship between (poly)phenols and gut microbiota can also impact elements related to biological rhythms, such as the circadian clock modulation, which ultimately can also affect brain function. Although evidence supporting this complex puzzle (Figure 1) is limited, some studies have begun to explore this link.

The interaction between dietary (poly)phenols and gut microbiota and its impact on cognitive and mood disorders, taking into account circadian rhythm modulation, has recently been approached. The authors concluded that (poly)phenols promote brain health and circadian rhythm maintenance through the gut-brain axis (Liu et al. 2023). In a recent study in C57BL/6J mice with circadian rhythm-related disorder, the neuroprotective effects of oolong tea (poly)phenols (OTP) intake (200 mg/kg BW) were associated with its capacity to modulate gut microbiota and their derived metabolites (Song, Ho, and Zhang 2024). In particular, intake of these (poly)phenols led to reduced microglia activation and reduction of neuroinflammation, neuron damage, and the neurotoxic metabolite glutamate. Moreover, an increased relative abundance of *Muribaculaceae* and *Clostridia_UCG-014*, decreased *Desulfovibrio*, and increased SCFA levels were observed. In addition, improving intestinal barrier integrity, which was correlated with decreased LPS levels in serum, was also reported. Interestingly, increased

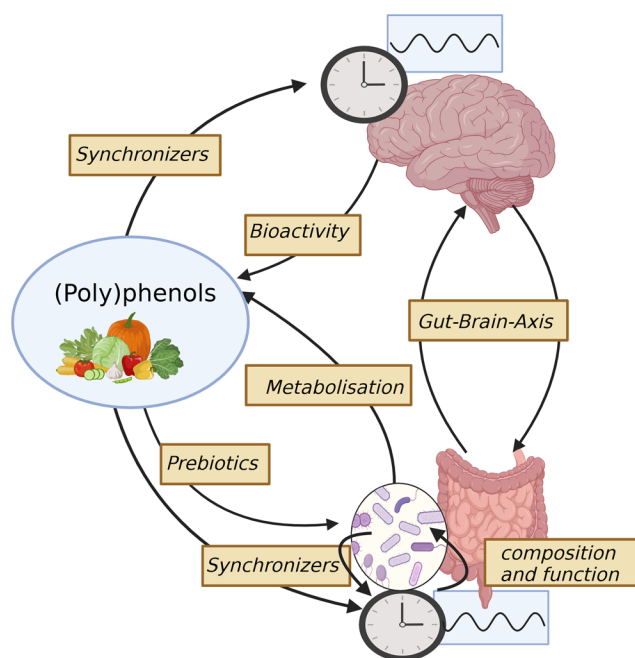


Figure 1. (Poly)phenols-microbiota-biological rhythms axis. Phenolic compounds act as synchronizers of the central and peripheral molecular clocks and modulators of gut bacteria (prebiotic effect). This leads to changes in gene expression and gut bacteria composition that will ultimately be translated into physiological and metabolic effects in the organism. Moreover, biological clocks and gut microbiota can also influence (poly)phenols bioactivities, the latest due to extensive metabolism in the colon. Additionally, gut microbiota can also synchronize host rhythms and has been shown to follow circadian oscillations, which are influenced by daily feeding patterns and affect both their composition and function. Therefore, this complex puzzle may significantly impact health, including brain function. In this regard, the gut-brain axis plays a significant role, serving as a pathway to deliver neuroactive metabolites produced due to this (poly)phenols-microbiota-biological rhythms axis.

BDNF levels were also observed. These results align with another study in mice, showing that intake of 0.1% OTP (w/w) alleviated gut microbiota dysbiosis and altered function induced by circadian rhythm disorder in mice. Moreover, OTP administration led to increased hypothalamic cell clusters, increased astrocyte and fibroblast numbers, and increased expression of clock genes, including *Cry2*, *Per3*, *Bhlhe41*, nuclear receptor subfamily 1 group D member 1 and 2 (*Nr1d1* and *Nr1d2*), D-box binding PAR bZIP transcription factor (*Dbp*), and retinoic acid receptor-related orphan receptor B (*Rorb*) in hypothalamic cells (Yan et al. 2024). In the study discussed above by Zhang et al. administering green tea (poly)phenols 0.1% (w/w) for 4 wks to C57BL/6J male mice subjected to circadian disruption led to amelioration of gut microbiota dysbiosis and regulation of bacteria-derived metabolites associated with brain nerves and circadian rhythms (Zhang et al. 2022). Hence, this study related the effect of these (poly)phenols on hypothalamic clock gene expression with effects on the gut-brain axis, which supports the link between these phenolic compounds, gut microbiota, and biological rhythms in the context of brain function. Another recent review highlights this link, describing the modulatory effects of tea (poly)phenols on circadian-related diseases and their bidirectional interaction with the gut microbiota (Yan, Ho, and Zhang 2022).

In another review also focused on tea (poly)phenols, authors discussed how these compounds could alleviate circadian rhythm disorder syndrome via the gut-liver-brain axis by regulating different components such as bile acids, tryptophan, or different receptors, including G-protein

coupled receptors, farnesoid X receptor (FXR) and aryl hydrocarbon receptor (AHR) (Hu, Luo, and Zeng 2023). Takeda G-protein coupled receptor 5 (TGR5), a bile acid receptor, which can be modulated by gut microbiota and (poly)phenols, has been described to affect clock genes in the suprachiasmatic nucleus in a cholemic mouse model (Zhou et al. 2025). Moreover, acute consumption of 30 or 60 mg/kg of chlorogenic acid improved cognition in a dose-dependent manner via regulation of gut microbiota in mice subjected to sleep deprivation, a condition closely related to circadian rhythm disruption, as previously discussed. In addition, it also prevented the formation of pro-inflammatory neurometabolites in the hippocampus and improved intestinal integrity in these mice (Zhu et al. 2024). In line with this, another review also investigated the connection between tea (poly)phenols, the circadian clock, and gut microbiota and its regulatory effects on circadian disturbances. The authors concluded that these (poly)phenols can improve sleep by modulating circadian rhythm through the gut microbiota (Xiang et al. 2023). Moreover, the gut microbiota-modulating effects of flavonoids from *Cyclocarya paliurus* (CPFs) (200 mg/kg) were also observed in the abovementioned study using a circadian rhythm disorder mouse model. Thus, in addition to modulating hypothalamic clock genes, the intake of these (poly)phenols also led to significant changes in gut bacteria abundance and derived metabolites. In particular, increased *Akkermansia* levels and decreased *Clostridiales* and *Ruminiclostridium* levels were observed (Sun et al. 2022). Authors also showed that gut microbiota-derived metabolites such as equol, agmatine,

N-acetyl-L-aspartic acid, lysoPE, lysoPC, choline, and 8-hydroxyadenine were altered in mice subjected to circadian rhythm disruption. Interestingly, supplementation with CPFs reversed this effect of constant darkness on some metabolites, decreasing lysoPE and increasing lysoPC and equol levels, which is associated with decreased risk of cardiovascular and neurodegenerative diseases. Equol, a blood-brain barrier permeable gut microbial metabolite of dietary isoflavone, is of particular relevance as it has been shown to exert neuroprotective effects, modulate microglia activation, and regulate the central circadian rhythm in ovariectomized rats (Nishimura et al. 2017; Subedi et al. 2017) and murine microglia cells (Subedi et al. 2017). In another study, administering 500 mg/kg of an apple (poly)phenol extract (APE) prevented alterations in clock gene expression caused by dextran sulfate sodium in C57BL/6 male mice. Interestingly, this effect was only observed when the extract was administered at ZT0 (beginning of resting phase). Additionally, APE decreased anxiety and depression-like behaviors by upregulating BDNF and postsynaptic-density protein 95 and decreased allograft inflammatory factor 1 (AIF1). The beneficial effects on behavioral disorders were more pronounced when APE was administered at ZT12 (beginning of active phase). Additionally, these APE effects on behavior and clock genes were accompanied by changes in gut microbiota, including increased Firmicutes/Bacteroidetes ratio and reduced relative abundances of *Escherichia-Shigella*, *Bacteroides* and *Parasutterella* (Qian et al. 2023).

Gut bacteria-derived metabolites may be one of the main drivers behind the connection between gut microbes, (poly)phenols, biological rhythms, and brain health. As previously mentioned, SCFAs have been shown to modulate the molecular clock, exert beneficial effects on brain function, and can be influenced by (poly)phenols administration (O'Riordan et al. 2022; Segers et al. 2019; Song et al. 2021; Tahara et al. 2018). Hence, these microbial metabolites have great potential as mediators of this interaction. Gut microbiota-derived tryptophan metabolites, such as indole derivatives, should also be considered. Thus, these metabolites follow circadian oscillations, play an essential role in the gut-brain axis, and can be modulated by (poly)phenols (Cryan et al. 2019; Gheorghe et al. 2024; Hu, Luo, and Zeng 2023; Yin et al. 2023). TMAO, a microbiota-derived metabolite whose capability to modulate circadian rhythms has been mentioned above, is also relevant in this context. Thus, this metabolite has been linked to impaired cognition, promotion of brain aging, and altered BBB function in mice (Hoyle et al. 2021; Li et al. 2018). Moreover, intake of a grape pomace polyphenolic extract (Taurisol®) inhibited the growth of TMA-producing bacterial strains and reduced TMAO levels in a randomized, placebo-controlled, cross-over study (Annunziata et al. 2019). Gut bacteria are also involved in the production of BCAAs, which are affected by (poly)phenols administration (Bartova et al. 2022) and circadian rhythms (Li and Seugnet 2025). These metabolites influence brain function by modifying large, neutral amino acid (LNAA) transport at the blood-brain barrier (Fernstrom 2005). In addition, neuroactive metabolites produced by gut

microbes such as GABA and 5-HT may also play a role in this complex puzzle as their levels can be modulated by (poly)phenols (Rebas et al. (2020) and preclinical studies have shown that they have a significant impact on the regulation of circadian rhythms in the suprachiasmatic nucleus (Dudley, DiNardo, and Glass 1998; Ono et al. 2018). The serotonin system has also been reported to affect the regulation of circadian gene expression in the mouse small intestine (Aoki et al. 2014).

Toll-like receptors (TLRs) may also play a significant role in the interaction (poly)phenols-microbiota-rhythms in the context of brain health. Thus, TLRs are pattern recognition receptors (PRRs) activated by bacterial amyloids and LPS, which are important for interacting with the host and the gut microbiota and maintaining intestinal homeostasis and integrity. It has been shown that circadian clocks are essential in integrating this dialogue between gut microbiota and TLRs to orchestrate homeostasis in the intestinal epithelium. Hence, the expression of TLRs has been demonstrated to be increased during the active phase and decreased during the resting phase in mice due to its modulation by ROR α and RevErb α (Mukherji et al. 2013). This opens a temporal window in which microbe-associated molecular pattern (MAMP) signals can be transduced by TLRs and has been linked to increased expression of genes involved in homeostatic functions during the active phase and the prevention of the disruption of the circadian clock in intestinal epithelium cells (IECs) (Mukherji et al. 2013). Interestingly, lack of microbiota led to alterations in clock genes, including ROR α and RevErb α , and therefore modifications in circadian oscillations of TLRs, which was linked to disruption of intestinal homeostasis (Mukherji et al. 2013). In addition, these receptors have also been shown to play a role in brain health. Thus, TLRs are also present in the brain, especially in the microglia, and have been associated with developing neurodegenerative disorders such as AD (Lin et al. 2019) and PD (Heidari, Yazdanpanah, and Rezaei 2022). In particular, TLRs can bind β -amyloid (A β) protein, leading to increased neuroinflammation and increased risk for these pathologies. Indeed, overexpression of TLR2 and TLR4 has been found in the brains of AD patients and mouse models of AD (Letiembre et al. 2009). However, TLR9 has been linked with a decreased risk of AD. Hence, TLR9 knockout mice showed impaired synaptic function (Patel, Patel, and McArdle 2016). Moreover, administration of TLR9 agonists decreased A β and tau pathologies, as well as levels of toxic oligomers in a mouse model of AD, which ameliorated the cognitive deficits of these mice (Scholtzova et al. 2014). It is worth mentioning that A β is similar to bacterial amyloids produced by gut microbiota and that LPS has been associated with increased levels of A β and cognitive deficits, highlighting a potential role of gut bacteria also in the development of neurodegenerative diseases via the gut-brain axis (Lin et al. 2019). Thus, disruption of gut microbiota-TLR signaling, such as that produced for circadian rhythm alterations, will increase intestinal permeability. This increases the circulating levels of bacterial amyloids and LPS, which can reach the brain, activating TLRs, triggering inflammation, and ultimately increasing the risk for cognitive disorders. Hence,

taking it all together, it seems clear that there is a link between gut microbiota, TLRs, circadian clocks, and brain function.

Interestingly, (poly)phenols have been found to modulate TLRs. For example, pomegranate peel (poly)phenols inhibited inflammation by suppressing the TLR4/NF- κ B pathway in RAW264.7 macrophages (Du et al. 2019; Kim et al. 2012). Moreover, tea (poly)phenols (300 mg/kg) were demonstrated to ameliorate cognitive decline in an aging model in rats by decreasing the neuroinflammation promoted by gut microbiota dysbiosis through the inhibition of the brain TLR4/NF- κ B inflammatory signaling pathway (Song et al. 2021). Flavonoids can also act as regulators of TLRs at different levels, including regulation of their gene expression, their activation, and the upstream and downstream signaling molecules involved in their pathway (Pérez-Cano et al. 2014). In addition, *in vitro* and *in vivo* studies have demonstrated that (poly)phenols can directly bind LPS (Wong et al. 2016) or decrease the LPS-binding protein (LBP) (González-Sarriás et al. 2018), preventing LPS interaction with TLRs (Wong et al. 2016). However, the role of biological clocks in this (poly)phenols-TLRs-microbiota interaction has not yet been investigated, and therefore, studies in this direction are needed.

Other relevant receptors that may also be involved in this complex puzzle are the nucleotide oligomerization domain (NOD)-like receptors (NLRs). These are intracellular pattern recognition receptors (PRRs) expressed in the gut and the brain that are involved in the transduction of gut microbiota signals. Indeed, activation of NLRs modulates different metabolic functions, significantly affecting several pathologies such as obesity, fatty liver disease, adipocyte differentiation, and adipogenicity (Bishehsari, Voigt, and Keshavarzian 2020). For example, it has been demonstrated that gut bacteria can modulate appetite and body temperature via the Nod2 receptor in mice (Gabanyi et al. 2022). Moreover, NOD2 in GABAergic neurons can recognize bacterial murpeptides, leading to reduced neuronal activity, loss of appetite, and altered thermoregulation. In addition, Nod-KO mice lacking both Nod1 and Nod2 receptors have also shown increased stress-induced anxiety, cognitive impairment, and depression, which was linked to impairments in the serotonergic pathway in the brain, decreased hippocampal cell proliferation and immature neurons, as well as reduced neural activation. These mice also showed increased gut permeability and alterations in intestinal serotonin signaling after exposure to acute stress (Pusceddu et al. 2019).

Circadian fluctuations of *Nod2* receptor expression have also been observed, with *ROR α* and *RevErb α* regulating its diurnal rhythmicity, similar to their role in regulating TLRs. Thus, a study in mice showed that *ROR α* and *RevErb α* bind the promoter region of the *Nod2* receptor gene, showing an antiphasic circadian profile. Moreover, *Nod2* receptor expression was decreased in antibiotic-treated mice (Mukherji et al. 2013). Regarding (poly)phenols, curcumin suppressed NF- κ B signaling via inhibition of Nod2 oligomerization in HCT116 cells (Huang et al. 2008). This polyphenol (40 μ M) also decreased the expression of the *Nod2* gene in fibroblast-like synoviocytes of rheumatoid arthritis patients,

leading to an anti-inflammatory effect (Akbari-Papkiadehi et al. 2023). Hence, given the critical role of NLR in the gut-brain axis, its modulation by the circadian clock, and its potential to be regulated by (poly)phenols, these receptors could be key players in the interplay between all these factors and, thus, further research focusing on unveiling this interaction is needed.

Another attractive potential candidate for mediating the link between (poly)phenols, gut microbiota, biological rhythms, and brain function modulation is the family of NAD(+)-dependent class III histone deacetylases (HDAC), also known as sirtuins (SIRT). SIRT1 is the most studied among the seven homologs identified in mammals and has been reported to be a key component in modulating biological rhythms. Thus, SIRT1 regulates the molecular clock-mediated chromatin remodeling and circadian control. Specifically, SIRT1 activates the transcription of the two major circadian regulators, BMAL1 and CLOCK (Chang and Guarente 2013). Indeed, the knockout of the *Sirt1* gene or pharmacological inhibition of SIRT1 activity leads to disturbances in biological rhythms and the acetylation of BMAL1 (Nakahata et al. 2008). In turn, circadian oscillation of the rate-limiting enzyme of the NAD⁺ salvage pathway, NAMPT, marks SIRT1 activity, which also controls key transcription factors and nuclear receptors essential in metabolism regulation. Indeed, this has been pointed out as a potential mechanism by which biological rhythms are coupled with metabolism. For example, SIRT1 facilitates the recruitment of different proteins to the promoter regions of genes involved in cholesterol metabolism and gluconeogenesis, such as the liver X receptor (LXR) for the former and PPAR γ coactivator-1 α (PGC-1 α) and Forkhead box O1 (FOXO1) for the latter (Stevenson and Lincoln 2017). Interestingly, SIRT1 is modulated by (poly)phenols (Ayissi, Ebrahimi, and Schluesener 2014) and has therapeutic potential against neurodegenerative disorders (Razick et al. 2023). Thus, activation of SIRT1 by resveratrol (30–50 μ M) has been shown to protect against the neurotoxic effect of amyloid- β accumulation in microglia through inhibition of the NF- κ B pathway (Chen et al. 2005). SIRT1 has also been linked to protective effects against neurodegenerative disorders, such as Parkinson's disease and amyotrophic lateral sclerosis, by upregulating autophagy (Song, Wu, and Zhao 2022). In addition, SIRT1 has been demonstrated to have potential against AD by inhibiting p53 (Wang et al. 2021). Moreover, SIRT1 is known to be involved in the age-related deterioration of the circadian clock (Chang and Guarente 2013). On the other hand, SIRT1 has been related to gut microbiota in different studies. Hence, C57BL/6 mice with disruption of *Sirt1* in the intestinal epithelium showed altered gut microbiota composition. Authors concluded that SIRT1 prevented intestinal inflammation by regulating gut microbiota, suggesting that this protein can mediate host-microbiome interactions (Wellman et al. 2017). Indeed, mice lacking SIRT1 catalytic activity showed increased Firmicutes/Bacteroidetes ratio (Caron et al. 2014). In a recent study, indole derivatives produced by gut microbiota attenuated neurodegenerative effects in both *in vitro* and *in vivo* aging models by modulation of the GPR30/AMPK/SIRT1 pathway (Yin et al. 2023). Hence, SIRT1 can

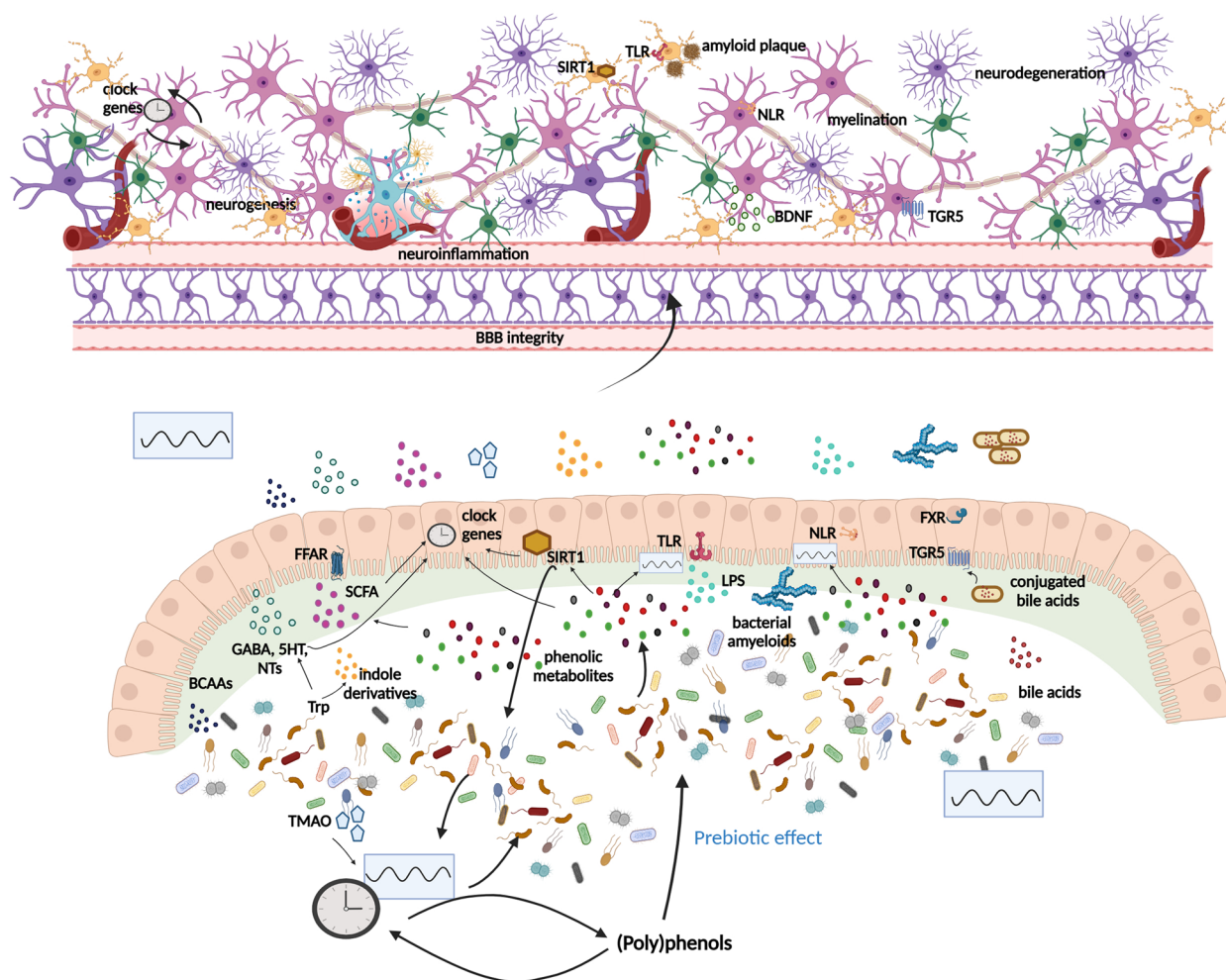


Figure 2. (Poly)phenols-microbiota-biological rhythms axis in brain function. Phenolic compounds reach the colon, where they undergo extensive metabolism by gut bacteria, producing various microbial-derived phenolic metabolites and altering the composition and functionality of the gut microbiota. These interactions are regulated by host rhythms, which modulate the diurnal oscillations of gut bacteria as well as the bioactivity and bioavailability of (poly)phenols. Changes in gut microbiota will lead to alterations in their derived metabolites, including microbial-derived phenolic compounds, TMAO, BCAAs, neuroactive metabolites such as GABA, 5-HT, and other neurotransmitters (NTs), SCFAs, indole derivatives, LPS, bacterial amyloids, and conjugated bile acids. These metabolites will enter the bloodstream and, eventually, reach the brain, where they regulate processes such as neurogenesis, neuroinflammation, myelination, and neurodegeneration through different mechanisms, including modulation of the central clock, levels of brain-derived neurotrophic factor (BDNF), amyloid plaque accumulation, and interactions with receptors such as Takeda G protein-coupled receptor 5 (TGR5), NOD-like receptors (NLRs), and Toll-like receptors (TLRs). Furthermore, some of these metabolites, including phenolic compounds, SCFAs, and 5-HT, can also influence the expression of clock genes in the intestine, thereby affecting the host's circadian rhythm system.

be behind the connection between (poly)phenols-gut microbiota-biological rhythms and its mediated effects on brain health.

5. Conclusions and roadmap

This review offers new insights into the intricate interplay between dietary (poly)phenols, gut microbiota, and circadian rhythms, highlighting their combined potential to impact brain health (Figure 2). Dietary (poly)phenols are xenobiotics, which undergo extensive metabolism through coevolutionary adaptations of the host and its gut microbiota, ultimately determining (poly)phenol health effects. These metabolic processes, shaped by each individual's unique gut microbial composition, underscore the importance of personalized approaches to fully harness the benefits of (poly)phenols.

One of the most intriguing aspects of the (poly)phenols-health relationship is the bidirectional interaction between (poly)phenols and biological rhythms. Circadian rhythms influence (poly)phenol bioavailability and activity, while (poly)phenols can, in turn, modulate circadian biology. This reciprocal dynamic can hold the key to significant neuroprotective effects, including reducing neuroinflammation, regulating hypothalamic clock genes, and enhancing gut-brain communication, crucial for maintaining cognitive function and mental health.

However, inter-individual variability in response to (poly)phenols, primarily driven by differences in gut microbial composition and specific metabolotypes, introduces another layer of complexity. Deciphering this variability is essential for identifying the microbial profiles and metabolites most beneficial to brain health and circadian rhythm regulation. Additionally, there is a compelling need to investigate how

the timing of (poly)phenol intake aligns with biological rhythms to optimize their effects.

The complex interplay between (poly)phenols, gut microbiota, and biological rhythms is mainly based on pre-clinical studies (animal and cellular models). In contrast, evidence in humans remains very limited. Thus, future research should focus on robustly designed human trials to validate preclinical findings. Integrating multi-omics approaches and longitudinal studies could offer deeper insights into the temporal dynamics of these interactions, particularly their role in preventing or mitigating neurodegenerative diseases.

The potential applications of this approach are relevant. Modulating circadian rhythms and gut microbiota disruptions (recognized contributors to neurological and metabolic disorders) by (poly)phenols could serve as the foundation for innovative dietary strategies and functional foods to support mental and cognitive health. Notably, such solutions would be effective and tailored to individual needs, ensuring long-term impact.

Achieving these ambitious goals will require collaboration across disciplines, joining expertise in microbiology, neuroscience, nutrition, and chronobiology. By addressing these critical areas, research can deepen our understanding of the intricate interplay between (poly)phenols, circadian rhythms, gut microbiota, and brain health, paving the way for groundbreaking advances in personalized healthcare.

Author contributions

C.T.F., J.C.E., and B.M.: conceptualization, writing—original draft, writing—review and editing. H.S. and J.E.C.: review and editing. J.E.C., J.C.E., and B.M.: funding acquisition. All authors contributed to the article and approved the submitted version.

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Data availability statement

No data was used for the research described in the article.

Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
AHR	hydrocarbon receptor
AIF1	allograft inflammatory factor 1
APF	apple (poly)phenol extract
BBB	blood-brain barrier
BCAAs	branched-chain amino acids
BDNF	brain-derived neurotrophic factor
BHIHE41	basic helix-loop-helix family member e41
BMAL1	brain and muscle arnt-like protein-1
CLOCK	circadian locomotor output cycles kaput
CSNK1D	casein kinase 1 delta
CPFs	Cyclocarya paliurus flavonoids
CRY2	cryptochrome 2
DBP	D-box binding PAR bZIP
FXR	farnesoid X receptor
GPX1	glutathione peroxidase 1
HPA	hypothalamic–pituitary–adrenal axis
LPS	lipopolysaccharide
MAMP	microbe-associated molecular pattern
NAMPT	nicotinamide phosphoribosyltransferase
NEUROD	neuronal differentiation 1
NLRs	NOD-like receptors
NR1D	nuclear receptor subfamily 1 group D
NRF2	nuclear factor erythroid-derived 2-like
NTs	neurotransmitters
OTP	oolong tea (poly)phenols
OTUs	bacterial operational taxonomic units
PD	Parkinson's disease
PER3	period 3
PRRs	pattern recognition receptors
SCFAs	short-chain fatty acids
SIRT	sirtuins
TGR5	Takeda G-protein coupled receptor 5
TLRs	Toll-like receptors
TMAO	trimethylamine N-oxide
T2D	type 2 diabetes
Uro-A	uroolithin A
5-HT	serotonin

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