Journal of Stress Physiology & Biochemistry, Vol. 21, No. 1, 2025, pp. 114-137 ISSN 1997-0838
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REVIEW

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Expression of circadian genes in dietary stress induced *Drosophila melanogaster*

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Received September 5, 2024

Circadian rhythm, the 24-hour cycles in physiological processes, are governed by circadian genes. In *Drosophila melanogaster* (fruit flies), these genes regulate various biological functions, including metabolism, sleep-wake cycles, and aging. This study explores the expression of circadian genes under different dietary stress conditions, including high fat, high sugar, high alcohol, high protein, and starvation diets. In *Drosophila*, Period, Timeless, Clock, and Cycle are the primary circadian genes, which play crucial roles in maintaining these rhythms. The regulatory mechanisms involve feedback loops where proteins encoded by these genes interact to regulate their own expression and that of other genes. Dietary stress can significantly impact circadian gene expression, leading to disruptions in the circadian clock and metabolic pathways. High fat and high sugar diets, for instance, can induce metabolic dysregulation and obesity, while high alcohol intake affects liver function and metabolism. Starvation and high protein diets also alter metabolic pathways, potentially impacting aging and lifespan. This study investigates these impacts at the molecular level, highlighting the intersection between dietary stress, circadian gene expression, and aging signaling pathways.

Key words: Circadian rhythm, Drosophila melanogaster, high sugar diet, high starvation diet, hyperglycemia, transcription based feedback loops

Circadian Rhythm (CR) is the general term for any modifications to behaviour, thought, or body that occurs within a period in organism, including mammals and cyanobacteria. An organism's daily activities are regulated by its internal clock to match the day/night cycle of its environment (Young & Kay, 2001). Although CR is a natural occurrence, it can be impacted by a variety of elements, including redox cycles, diet, temperature, and light (Johnston *et al*., 2016). The suprachiasmatic nucleus (SCN), which controls a variety of neuronal and hormonal pathways, houses the mammalian core clock and establishes synchronization involving the external tissues and internal clock (Albrecht, 2012) The *Drosophila melanogaster* Central clock is located in the organ of Bolwig, which is located inside the cerebral cortex, and it remains active over the whole life cycle. An auto-regulatory feedback system composed of circadian genes and their products aids in sustaining a rhythmic oscillation that lasts 24 hours. CR controls a variety of physiological and behavioral processes in *Drosophila*, including eclosion, temperature sensitivity, and courting behavior (Kaneko *et al*., 2012). Thus, metabolic and physiological abnormalities in *Drosophila melanogaster* are caused by any disruption in CR, whether as a result of faulty genes or external stimuli. Mammals with similar phenotypes have higher rates of cancer, aging, atherosclerosis, neurodegeneration, obesity, and diabetes, among other illnesses (Barnea *et al*., 2010; Masri *et al*., 2015; Videnovic *et al.,* 2014). One of the most common and long-lasting metabolic conditions of our day is diabetes, which is brought on by either insulin resistance or inadequate insulin secretion, which raises blood glucose levels. Furthermore, obesity increases the likelihood of developing type 2 diabetes(T2D), which is a complex condition with various etiologies. A popular model organism for researching the basic metabolic regulation mechanisms underlying a variety of illnesses, including diabetes and obesity, is the *Drosophila faunus* (Alfa & Kim, 2016). The likelihood of developing type-I diabetes is increased by obesity, which has been frequently associated with insulin resistance. T2D is known to be caused by lipid oxidation abnormalities as well (Kahn *et al*., 2006). It's interesting to note that there are several notable parallels between the mammalian and *Drosophila melanogaster* insulin pathways (Álvarez-Rendón *et al.,* 2018). The insulin receptor, insulin growth factor, and adipokinetic hormone signaling are all conserved components of the insulin system (S. K. Kim & Rulifson, 2004), there are some distinctions. For example, whereas both growth and metabolism are regulated by the same gene in *Drosophila*, they are regulated by different genes in mammals. Despite this, *Drosophila melanogaster* continues to be a great model to study circumstances similar to diabetes (Álvarez-Rendón *et al*., 2018).

Diabesity, which is a term used to describe the interdependence of obesity and Type 2 diabetes is distinguished by a decline in liver glucose production, insulin-mediated glucose transport, and peripheral tissue glucose metabolic process (Kahn *et al*., 2006). According to the previous study, 9% of the human population is at higher risk of obesity and type 2 diabetes (T2D) if they consume a high-fat diet (Heinrichsen *et al*., 2014). Similar to this, a diet that is heavy in fat or sugar causes hyperglycemia in *Drosophila melanogaster* (Song *et al*., 2017). The flies fed a diet heavy in sugar exhibited hyperglycemia in a manner akin to that of flies fed HFD (Heinrichsen & Haddad, 2012) and mutant flies with insulin-producing cells (IPCs) (Rulifson *et al*., 2002a; Song *et al*., 2010) . Much research has to be done, despite a wealth of literature suggesting a connection decreased CR and problems in Physiology, behavior, and metabolism in a variety of species (Johnston, 2014; Maury *et al*., 2010). Previous studies have also suggested that diabetes is a result of disruptions to the y clock, and that individuals with diabetes also have abnormalities in their circadian rhythm (Kadono *et al*., 2016; Lee *et al*., 2015). Although there is evidence linking circadian rhythm to the overall status of diabetes, it is yet unknown if irregularities in the circadian rhythm cause metabolic illness to begin, develop, or worsen (Javeed & Matveyenko, 2018). Some data in *Drosophila melanogaster* suggests that whereas Mutants of the insulin peptide and the insulin receptor exhibit fragmented sleep and dysrhythmia in

foxo or shaggy mutants (Martinek *et al*., 2001a; Metaxakis *et al*., 2014; Zheng *et al*., 2007)**.**

Core circadian genes and their functions

Konopka found that every mutation he found corresponded to a single gene, which he named period. These mutations included those that had rhythms that were entirely deleted, shortened (to 19 hours), or prolonged (to 28 hours) in terms of periodicity. While per was the sole known circadian gene for a considerable amount of time, gradual advancements research conducted in the 1990s resulted in the discovery of timeless (Sehgal *et al*., 1995), clock (Allada *et al*., 1998a), and cycle (Rutila *et al*., 1998), which together with per constitute the primary transcriptional feedback loop that generates circadian rhythms. Late 1990s and early 2000s, cryptochrome, often known as cry, was identified as a circadian photoreceptor (Emery *et al*., 1998). Additional findings included the kinases double-time (Martinek *et al*., 2001b) as well as vrille, a transcription-activating factor connected to a different feedback loop. (Blau & Young, 1999).

In *Drosophila melanogaster*, the core circadian genes and their functions are crucial for regulating the biological clock.

1. **Period (*per*):** The *per* gene is involved in the negative\ feedback mechanism of the circadian rhythm. It encodes the PER protein, which accumulates in the cytoplasm during the night and inhibits its own transcription by forming complexes with other proteins like TIM (Timeless). This regulation controls the timing of the circadian rhythm (Hall, 2003).

2. **Timeless (t*im*):** The t*im* gene works in conjunction with per to regulate circadian rhythms. It encodes the TIM protein, which forms a complex with PER in the cytoplasm. This complex inhibits the activity of the CLOCK-CYCLE transcription factor complex, thereby influencing the expression of clock-controlled genes (Price *et al*., 1998).

3. **Clock (*clk*) and Cycle (*cyc*):** The *clk* and *cyc* genes encode the CLOCK and CYCLE proteins, respectively, which form a heterodimeric transcription factor complex. This complex activates the transcription from the genes tim and per, thus initiating a positive feedback loop that drives circadian rhythms (Allada *et al*., 1998a).

4. **Cryptochrome (*cry*):** The *cry* gene encodes the CRYPTOCHROME protein, which is involved in photoreception and resetting the circadian clock in response to light cues. It interacts with the TIM protein to regulate its degradation, thereby influencing the period length of the circadian rhythm (Stanewsky *et al*., 1998).

The clock molecular mechanism

Transcription-based feedback loops: The idea that the PER protein negatively regulates its own transcription to create an auto regulatory circadian loop was developed in response to the discoveries that both per RNA and protein are expressed cyclically and that rising levels of protein are linked to falling levels of mRNA (Siwicki *et al*., 1988; Zerr *et al*., 1990). Further research validated this idea by demonstrating that the two mRNAS cycle in phase and that transcription is directly influenced by the direct interaction of the PER and TIM proteins (Gekakis *et al*., 1995). The foundation of overt rhythms in *Drosophila melanogaster* is the negative feed-back loop that is thus produced. As will be shown later, additional components must be included in the loop's maintenance. Per and Tim mRNA levels increase reach their zenith in the early evening during the day. From this juncture over the course of the evening, the two proteins begin to amass, first in the cytoplasm and subsequently in the nucleus (Zheng & Sehgal, 2012). Stabilizing Peroxisomal excretion requires TIM for its transport to the nucleus According to (Jang *et al*., 2015), certain importins also regulate the location of the two proteins in the nucleus and this regulation it seems to be time-dependent (Curtin *et al*., 1995).

Figure 1 shows the reduction in PER and TIM's mRNA levels caused by the proteins' negative autoregulatory feedback is correlated with their nuclear localization. While PER and TIM is unable to bind DNA, they can control transcription by blocking Clock and Cycle, two of their transcriptional activators. Biochemical evidence supports the PER's sequester of the CLK–CYC complex from DNA and a hypothesis in which it enlists the kinase DBT (aCK1e homolog) to stimulate CLK phosphorylation are both plausible, even if the

mechanics of negative feedback remain poorly understood (E. Y. Kim & Edery, 2006; Nawathean *et al*., 2007) . It is unclear what part TIM plays in unfavorable reviews. Early in the morning sees a large reduction in TIM levels, PER expression has also dramatically dropped by midafternoon, lifting the unfavorable comments and enabling a fresh transcription cycle. Beyond the primary feedback loop mentioned previously, the *Drosophila melanogaster* clock also has a secondary loop that is synchronized with the primary loop (Cyran *et al*., 2003) state that the CLK–CYC complex in this loop causes the expression of Clk to be repressed by Vrille (VRI) and transcriptionally activated by PDP1. By giving a rhythmic feedback on Clk expression, PDP1 and VRI maintain the rhythmic expression of Clk mRNA. However, as CLK protein levels do not cycle, the cause of the mRNA cycling is unknown (Houl *et al*., 2006). According to (Glossop *et al*., 2003), the second loop is intended to increase the system's precision and stability.

Mammals and insects both have similar transcriptional feedback loop regulation mechanisms, but they also have similar clock gene functions. Human circadian disruption Advanced Sleep Phase Disorder has been associated with bovine Per2 and CK1d, homologs of genes originally linked to fruit fly circadian rhythms, according to studies by (Toh *et al*., 2001; Xu *et al*., 2005). The functions of homologs of CLK, CYC (also referred to as BMAL1 in humans), and PER in mammals are similar to those in *Drosophila melanogaster* (Partch *et al*., 2014). Though, as mammals' The clock receives light input as supplied not belonging to a cell through Renal ganglion cells that are inherently photosensitive (Güler *et al*., 2008), the closest mammalian homolog of CRY seems to be acting like TIM, working with PER to suppress its own transcription, rather than acting as a photoreceptor. It appears that some insects, like butterflies and honeybees, possess a CRY similar to that of mammals, which can function as an antagonistic transcriptional regulator. This suggests that the mammalian CRY is a remnant of the evolutionary past, even though it appears to have disappeared in *Drosophila melanogaster* (Rubin *et al*., 2006). An additional transcriptional feedback loop in mammals is comparable within the fly PDP1/VRI loop (Partch *et al*., 2014).

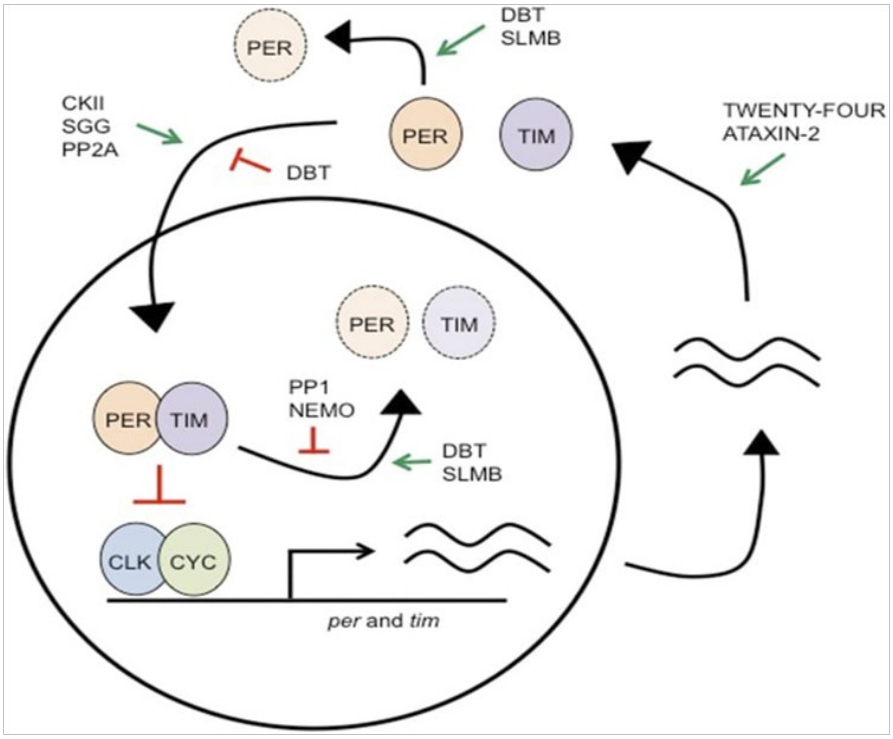

Table 1: Expression of period and timeless genes and its molecular feedback loop
Courtesy: https://images.app.goo.gl/XtVmWnXwakMWtvJB7

Regulatory mechanism of circadian gene expression

Higher eukaryotes' circadian clock is thought as a preserved self-regulatory feedback mechanism for transcription and translation that is regulated by rhythmic transcriptional activation and repression. The circadian clocks of mammals and some groups are based on interlocking transcriptional feedback loops that activate transcription by using fundamental helix-loop-helix and Per-Arnt-Sim heterodimers are important transcription factors (Partch *et al*., 2014). A heterodimer made up of CYCLE (CYC) and CLOCK (CLK) functions as the main transcription factor in the fruit fly *Drosophila melanogaster's* clock circuit (Allada *et al*., 1998b; Rutila *et al*., 1998). When CLK/CYC associates It binds DNA using a conventional Sequences that resemble the E-box CACGTG (Darlington *et al*., 2000; Hao *et al*., 1997; McDonald *et al*., 2001)**.** In particular, circadian biology is interested in the identification of transcripts that are regulated by CLK/CYC. However, since the sequence pattern is found across the fly genome, e-boxes are not very good markers of potential clock-regulated genes. Conversely, the atoms that make up surrounding the either the E-box or a pattern multiple similar themes spaced near together likely increase synchronize transcriptional process, Particularity of TFs, and improved bonding propensity (Kyriacou & Rosato, 2000; Muñoz *et al*., 2002)**.** Circadian transcriptional control in *Drosophila melanogaster* requires Ebox-dependent enhancers, according to investigations on the areas where two clock genes are promoted that are known to be present: period (per) and timeless (tim). As far as circadian enhancer motifs go, the per promoter has probably been explored the most. An enhancer, which stimulates the production of genes related to circadian rhythmsis a 69-base pair tract located beyond the start point of transcribing (Hao *et al*., 1997). The production of substantial amplitudes and tissue-specific expression by this enhancer is dependent on three sequences near the E-box, while transcriptional activation is mediated by an E-box motif (Hao *et al*., 1997; Lyons *et al*., 2000). A 18-bp region with an E-box that can recapitulate per spatial and temporal expression.(Darlington *et al*., 2000). According to (McDonald *et al*. 2001), the TIM promoter is outfitted with closely spaced E- and TER boxes, a version of the widely used E-box sequence. The two non- original E-boxes, TER1 and TER2, are required for this time enhancer to significantly start the cycle and activate gene expression. Standard E-box included with the accentuater does not seem to work well enough by itself, suggesting that the TER boxes are required to get it to work. More resources for identifying the components in charge of transcriptional control have become available as a result of growing understanding complete cDNAs that have been cloned and annotated, transcription initiation points and locations where transcription factors bind of the *Drosophila melanogaster* genome (Adams *et al*., 2000; Stapleton *et al*., 2002)**.** In a previous investigation, it was discovered that the 69 bp per enhancer contained a similar motif made up of two closely spaced E-box-like components and other CYC/CLK-regulated genes. In response to our earlier findings, a second distinct and separate theme of 29 bps. As the current paper describes the latter motif, also referred to as "CATAC," which stands for Clock-Associated Transcriptional Activation Cassette, and the facts about expression in space and time it provided (Paquet *et al*., 2008).

Effect of high-fat diet on lifespan, metabolism, fertility and senescence behaviour in Drosophila

Consumption a high-fat diet to increase your chances of becoming obese, which in turn increases your chances of developing diabetes, cancer, heart disease, as well as additional metabolic illnesses. (Bray & Popkin, 1998; Dietrich *et al*., 2013; Musselman & Kühnlein, 2018)**.** There is a connection between obesity and a higher risk of cognitive impairment (Hwang *et al*., 2010; Liu *et al*., 2015)**.** Since it has a short life span and is easily raised in big numbers, the fly with genetic tractability A fascinating organism for studying how nutrition affects metabolism, behavior, aging, and lifespan is the *Drosophila melanogaster* (Heier & Kühnlein, 2018a; Owusu-Ansah & Perrimon, 2014a). Because approximately 65% of the genes linked to human disease have functional orthologs in flies Moreover, *Drosophila melanogaster* has been used to model a number of human diseases (Ugur *et al*., 2016) **.**

Recent research has shown how the HFD affects the physiology and overall health of *Drosophila melanogaster* (von Frieling *et al*., 2020) **.** While some of this research looked at the impact of HFD on lifespan, the majority of these studies focused on the consequences of very brief exposure to HFD, lasting one to three weeks (Rivera *et al*., 2019) **.** Previous research has demonstrated that a excessive fat intake substantially shortens the life expectancy of flies, both male and female, (Woodcock *et al*., 2015) and negatively impacts their climbing behavior, short-term phototaxis memory, and behavioral reactions to smell (Rivera *et al*., 2019) **.**

Insulin signaling, glucose homeostasis, negative geotaxis, cardiac function, and gut physiology are all negatively impacted by even a brief exposure to a low-fat diet (HFD), lasting only one week (Birse *et al*., 2010a)**.** It just takes five days of high-fat diet (HFD) exposure for flies to become more susceptible to famine, resulting in an increase in the hyperactivity caused by fasting (Huang *et al*., 2020)**.** Moreover, it has been demonstrated that the HFD alters the transcription of genes related to cell signaling, memory, metabolism, olfaction, mitosis, and motor function (Rivera *et al*., 2019)**.** It is unclear how a high-fat diet affects *Drosophila melanogaster* physiology and longevity negatively. Lipids are necessary for the manufacture of signaling molecules, the assembly of cellular membranes, energy metabolism, and, in adult female flies, oogenesis in particular (Toprak *et al*., 2020)**.** Since TAG is scarce in the *Drosophila melanogaster* natural diet, carbohydrates are a primary dietary source of stored lipids. The stomach and fat body subsequently convert these carbs into TAG (Heier & Kühnlein, 2018a). Nevertheless, many lab diets contain lipids, and *Drosophila melanogaster* is equipped with taste receptors that can identify free fatty acids, (Ahn *et al*., 2017). When FFA levels are low, these receptors mediate attraction; when levels are high, repulsion results, as seen by the proboscis extension reflex, a reflexive feeding response (Masek & Keene, 2013). It would seem like flies should be able to control how much FFA they eat. However, When flies are subjected to synthetic HFD made from coconut oil, which is primarily made up of FFAs, for an extended period of time, their FFA sensing appears to be dysregulated or overridden.

Therefore, in order to reduce the negative consequences of increasing dietary FFA intake, flies must mount a reaction. In examining the immediate and long-term impacts of high-fat diet (HFD) on *Drosophila melanogaster* physiology and longevity, the female flies, whether virgin or mated, exposed to HFD have shorter lifespans and have a faster aging-related loss in their capacity to climb. Three weeks on a high-fat diet (HFD) causes a reduction in fecundity in virgin females, and sleep fragmentation is higher in these females than in controls. A storage organ connected to the foregut, the crop, grows larger after prolonged exposure to a high-fat diet. Based on Nile Red staining, it appears that the distended crops retain fats.

It astonished us that there were no consequences of a high-fat diet over time on body mass triacylglycerids (TAG), glycogen, or glucose levels. Conversely, mated flies that were fed a high-fat diet for a week showed increased TAG and decreased body mass. The mobilization of stored lipids for energy during exercise or fasting is regulated by adipokinetic hormone (AKH), which functions similarly to glucagon in insects (Grönke *et al*., 2007; Heier & Kühnlein, 2018a; Toprak *et al*., 2020). On the other hand, a number of *Drosophila melanogaster* insulin-like peptides regulate lipogenesis and the storage of fat after feeding (Heier & Kühnlein, 2018a; Toprak *et al*., 2020)**.** Thus, at the transcript levels of Akh and dilp in flies fed a high-fat diet (HFD) and found that whereas dilp transcripts remained unchanged, Akh transcript levels increased**.** Lastly, since HFD-fed flies had higher levels of Akh transcripts, AKH may control the impact of HFD on fertility and lifespan. When compared to control flies, akh mutant flies exhibit longer lifespans; nevertheless, both mutants and controls have shorter lifespans when on HFD. Even Nevertheless, both short- and long-term HFD lowers fecundity in both mutants and controls. Additionally, fertility is affected in Akh mutant flies.

Taken together, our findings show that a high-fat diet (HFD) decreases enhances AKH signaling, lowers the amounts of the synthesising enzyme tyrosine hydroxylase in dopaminergic neurons, and negatively

impacts longevity, sleep, negative geotaxis, and fertility. Additionally, it appears that the crop may significantly affect the body's response to a diet rich in fat.

Impact of high sugar diet in Drosophila

Hypoglycemia in Drosophila melanogaster caused by a high-sugar diet

A high-calorie meal with elevated protein, fat content, or sugar content to wild-type Canton-S *Drosophila*, while maintaining the same amounts of all other ingredients. Comparable to a banana in terms of proportion, According to (Carsten *et al*., 2005) 86.4% of the calories in the high-sugar diet were from carbs. Invertebrates on the elevated glucose diet consumed fewer calories than the larvae on the high-fat and -protein diets, but in comparison to other high-calorie diets, they acquired greater blood glucose levels or more severe hyperglycemia. Trehalose is a glucose disaccharide that is created from intracellular glucose in fat body cells and released into the hemolymph. Chow raised their blood sugar levels to get similar results. According to (Rulifson *et al*., 2002b; Song *et al*., 2010), Trehalose levels increased in a manner reminiscent of that seen in *Drosophila melanogaster* with low or no insulin. Conversely, there was a decrease in glycogen levels in larvae fed an excessive sugar intake. Insulin pathway mutants and glycogen levels decreased in a comparable manner (Böhni *et al*., 1999; Shingleton *et al*., 2005)

Insulin resistance was the outcome of high-sugar diet

The investigation into the reason behind hyperglycemia in larvae fed a lot of sugar by examining two traits: developing rate and larval size, both of which depend on insulin signaling (Böhni *et al*., 1999; Chen *et al*., 1996). Fly eggs develop into larvae, which feed continuously for the duration of their life cycle before molting twice to reach the first and second instar stages (L1 and L2). Following 5-7 days of laying eggs, third-instar (L3) larvae "wander" as they prepare to mature into adult flies, leaving behind their meal. Wild-type roaming L3 larvae fed high-sugar, high-fat, or high-protein meals showed a reduction in size despite consuming more calories; the animals fed high-sugar diet showed the most reduction in size. Additionally, compared to adults raised on control food, those raised on high-sugar meal were smaller. Similar to flies with IPC ablation (Rulifson *et al*., 2002b) or changes that decreased the amount of insulin receptor activation (Chen *et al*., 1996; Shingleton *et al*., 2005), the animals fed on high sugar showed reductions in both larval growth rate and size. Surprisingly, high-sugar feeding resulted in a significant 3-5 day delay in the larval growing rate when compared to those maintained on control chow. In order to accommodate for the development's slower rate, the requirements for carbs were loosened because glucose, fructose, and maltose all produced results that were comparable. Remarkably, the presence of disaccharides was observed about half the osmolarity of the monosaccharides, indicating that the delays linked to high sugar levels were probably not caused by the food's osmolarity. To confirm that the traits shown in larvae kept at high sugar concentrations weren't the consequence of a protein deficiency, examined the altered the diet's protein content so that each animal received the same amount. None of the phenotypes caused by sugar were saved by this. Since hyperglycemia, larval size, and developmental rate were most significantly impacted by high-sugar eating among high-calorie diets. With the exception of a few instances, lasting physiological alterations brought on by the high-sugar diet were investigated using roaming L3 larvae. The larvae are no longer feeding at this point since they have grown to their maximum size. Because the insulin signaling system performs IGF- and insulin-like tasks in the fly, both insulin-resistant and insulin-deficient *Drosophila melanogaster* exhibit growth abnormalities (Baker & Thummel, 2007). Examination of high-sugar eating, caused peripheral insulin resistance or insulin insufficiency. The raised DILP2-GAL4 and UAS-GFP *Drosophila melanogaster* under either a high-sugar or control condition diet in order to evaluate IPC integrity. There was no discernible change in the quantity or appearance of IPCs. Nevertheless, following a prolonged high-sugar diet, the expression of several genes producing DILPs rose, indicating that the larvae tried to raise their DILP levels in an attempt to offset the higher glycemic load. Since diet has been demonstrated to regulate insulin secretion via IPCs (Géminard *et al*., 2009), the study was carried out using DILP2-GAL4,

UAS-DILP2-FLAG larvae to measure the amounts of circulating DILP. When compared to larvae raised on control diet, the hemolymph of larvae raised on high sugar had higher amounts of FLAG-tagged DILP2. These findings suggested that peripheral insulin resistance was a fundamental problem upon high-sugar feeding, and they also showed that the hemolymph of larvae raised on high sugar was not insulin deficient. Evaluating the efficacy of exogenous insulin to induce Akt phosphorylation at position Ser505 in order to measure insulin resistance. This residue functions as a marker of the activity of the insulin system and is analogous to Ser473 in mammals. When exposed to Human insulin recombinant at 0.5 µM, wandering L3 larvae fed a control diet showed an average 2.8-fold increase in phospho-Akt. In comparison to controls, larvae fed a high-sugar diet showed a markedly reduced sensitivity to insulin. When combined, the traits of insulin-defective growth phenotypes, hyperglycemia, and insulin resistance are indicative of a type 2 diabetes model in larvae fed high sugar.

Impact of high alcohol diet in Drosphila

Numerous studies have been conducted on *Drosophila melanogaster* to examine developmental processes and the functioning of the neural system. By doing this, scientists have discovered a large number of Mammalian homologs, or their analogous *Drosophila melanogaster* gene products, have been proposed as potential targets for alcohol. Because instance, homologs of the neurotransmitter receptors for gamma-aminobutyric acid, serotonin, dopamine, and glutamate are found in flies (Littleton & Ganetzky, 2000). These neurotransmitters have all been linked to the effects of alcohol (Tabakoff & Hoffman, 1996). Therefore, *Drosophila melanogaster* could be a good model to examine how alcohol affects brain function and behaviors associated to alcohol, like tolerance and susceptibility to its effects. The experimental methods for measuring alcohol sensitivity are described in this article together with the preliminary findings of *Drosophila melanogaster* alcohol-related genetic studies.

Measuring alcohol sensitivity in Drosophila

Fermenting plants, or those with three percent or higher alcohol content, are part of *Drosophila's* natural habitat. Fruit flies may thus effectively metabolize alcohol to use it as a starting material for the synthesis of lipids or as an energy source, making them immune to the harmful effects of alcohol (Geer *et al*., 1993) Alcohol is introduced by researchers to the fly culture medium are fed in order to determine whether a specific *Drosophila melanogaster* strain is immune to the harmful effects of alcohol (Geer *et al*., 1993). According to these findings, there are differences in the alcohol resistance of *Drosophila melanogaster* strains that have been obtained from the wild (Kamping & van Delden, 1978). Moreover, in a laboratory context, researchers found that they could quickly and dramatically increase the alcohol tolerance of a *Drosophila melanogaster* population. By carefully breeding flies that were resistant to the effects of alcohol vapour (Cohan & Hoffmann, 1986) or that survived exposure to high alcohol levels in their diet (Chambers, 1991), for example, resistant strains were created.

When exposed to vaporized alcohol, adult *Drosophila melanogaster* display a number of symptoms, including as diminished motor control, that are comparable to acute intoxication in mammals. Scientists placed flies in a small area with grid lines to measure the effect of alcohol on flight. To measure locomotor behavior, one can look at the number of grid lines crossed over time (Singh & Heberlein, 2000). After being exposed, the flies exhibit drowsy and uncoordinated behavior, followed by hyperactivity and confusion in a matter of minutes. When exposed for roughly 20 minutes, they grow motionless; however, they recover in 5 to 10 minutes when the alcohol is removed (Singh & Heberlein, 2000).Research revealed that dopaminergic systems, or nerve-cell systems that use the neurotransmitter dopamine, regulate the locomotor-stimulating effects of alcohol in mice (Phillips & Shent, 1996). Researchers employed the above-described test on flies with much lower dopamine levels to look for alcohol-induced alterations in locomotor behavior in order to investigate a possible function for

dopamine in *Drosophila melanogaster* alcohol reactions. While alcohol produced sedation was normal in these flies, it was far less effective at inducing locomotor activity (Bainton *et al*., 2000). Based on these observations, it appears that *Drosophila melanogaster* and rodents respond to acute alcohol exposure in ways that are similar in terms of their dopaminergic systems.

Using an inebriometer to measure the incapacity of *Drosophila melanogaster* to stand following alcohol consumption is another method of assessing the effects of alcohol on the species. This device, which was initially created to grow flies immune to alcohol selectively (Weber & Diggins, 1990) consists of a 125 cm vertical tube with several sloping mesh baffles that allow flies to perch. The flies are then made drunk by passing alcohol vapor through the tube. The flies thus lose their ability to maintain their posture and start to fall through the tube. The amount of time it takes them to emerge from the bottom of the tube at a specific alcohol concentration indicates how sensitive they are to alcohol consumption. Therefore, flies that are more susceptible to the loss of postural control caused by alcohol come out of the tube sooner than flies that is more resilient to the effects of alcohol.

Impact of high protein diet in *Drosophila*

Protein restriction diets (PRDs) are dietary interventions that lower protein intake without putting a person at risk for malnutrition (Green *et al*., 2022). Previous researches have documented the advantages of PRD, including enhanced lifespan, treatment of chronic disorders, and betterment of overall organism welfare (Ferraz-Bannitz *et al*., 2022). Dietary patterns associated with longevity, including the Guangxi and Okinawan patterns (which consist of 85% carbohydrates and 9% protein), have been linked to Parkinson's disease (PRD) (Han *et al*., 2022; Kitada *et al*., 2018). According to the throwaway soma idea, PRD's life span benefits result from the transfer of scarce energy sources, spanning from sexual reproduction to bodily upkeep (Shanley & Kirkwood, 2000). Living and procreating in the context of PRD, however, appear to be influenced by the harmony of the macronutrients in food rather than the total calorie the diet's composition, according to recent research (Zanco *et al*., 2021). Furthermore, research indicates that deficiencies in particular amino acids, consisting of branch chain amino acids, tryptophan, and methionine, may have an indirect impact on the restorative and beneficial effects of PRD (Grandison *et al*., 2009; Orentreich *et al*., 1993; Segall & Timiras, 1976). Disease and shortened life spans can result from these protein building blocks ' interactions adding additional amino acids or byproducts, which can impair the molecular and physiological homeostatic activities of several organs, whole organisms, and/or organisms (Grandison *et al*., 2009). It is expensive to maintain mammalian models to simulate metabolic conditions; the use of *Drosophila melanogaster* illness models is growing (Asiimwe *et al*., 2022). Compared to mice, which takes months to get obesity, *Drosophila melanogaster* develops lipids in both fat and non-fat tissue in a manner that is depending on dosage in a shorter amount of time (Birse *et al*., 2010b). *Drosophila melanogaster* contains the majority of the critical metabolic enzymes found in mammals, as well as highly conserved genes that control lipid metabolism (Owusu-Ansah & Perrimon, 2014b). Similar to how triglycerides are kept in the adipose tissue of mammals, lipids are kept in *Drosophila's* adipose tissue as triglycerides (DiAngelo & Birnbaum, 2009). Furthermore, the molecular process governing the process via which cellular lipid droplets metabolize neutral lipids is similar to the lipoprotein pathways in mammals (Palm *et al*., 2012). Similar to other insects, *Drosophila melanogaster* stores different types of sterols based about dietary fat sources and sterol requirements, including ergosterol, stigmasterol, zymosterol, and campesterol being given an HFD (high-fat diet) (Liu & Huang, 2013). Dietary sterols are converted to triglycerides, which are the primary circulation and fat reserves for storing, fat reserves for storing, based on the metabolic needs and energy balance for many bodily functions (Heier & Kühnlein, 2018b). The term "obesity" in flies refers to increased accumulation of fat rather than a specific measurement, unlike humans, who are deemed obese at a Body Mass Index of ≥ 30.0 kg/m2 (Gáliková & Klepsatel, 2018). PRD, or protein restriction, is the term used in the context of *Drosophila melanogaster* obesity modeling research, where yeast is the main protein source (Simmons & Bradley, 1997). Male flies are

frequently chosen over female flies due to their higher consumption of carbohydrates and subsequent accumulation of fat (Vargas *et al*., 2010).

The "thrifty gene" theory states those 30,000 years ago, individuals survived better during times of hunger and starvation due to the accumulation of energy during prosperous times. This is how obesity initially emerged (Haslam, 2007; NEEL, 1962). The idea of the "Obesity paradox" (Park *et al*., 2014) stems from the observation that whereas a BMI of > 30 kg/m 2 is associated with a rise in all-cause mortality (Flegal *et al*., 2013), while a BMI of 25 < 30 kg/m 2 is connected to a fall in deaths from all causes (Di Angelantonio *et al*., 2016) and a better prognosis for disease. The preventive functions of obesity considering the fact that elevated adiposity exists independently of the known harmful consequences of obesity, like a rise in co-morbidities and mortality associated with obesity, are also being revealed by obesity research employing *Drosophila melanogaster* (Lushchak *et al*., 2011) . On the other hand, these have been linked to ectopic lipid accumulation, reduced rate of fat turnover, glucotoxicity, and build-up of lipid autotoxins during fly development (Wen *et al*., 2018). Lipid accumulation caused by autotoxins, ectopic fat growth, low fat turnover, and glucotoxicity interact with several biological processes, including those that control gene expression, energy homeostasis, cellular stress regulation, pro-inflammatory cytokine regulation, and Protein kinase II reliant on calcium and phosphoinositol-3-protein kinase/Akt pathways; these processes include the Jun-N-terminal kinase pathway and the Adenosine Monophosphate Protein Kinase pathway (Dias *et al*., 2018; Wen *et al*., 2018). This in turn disturbs regular multi-organ cellular homeostatic processes because of elevated mitochondrial and endoplasmic reticulum stressors. These results in a host of detrimental effects linked to obesity, such as the formation of foam cells, increased production of cytokines, insulin resistance, and hypoxia. These can be clinically manifested as dyslipidaemia, polycystic ovarian syndrome, type II diabetes, osteoarthritis, some malignancies, coronary artery disease, stroke, hypertension, liver disease, and psychiatric problems (Pillon *et al*., 2021).

Despite the fact that *Drosophila melanogaster* is a very good model for obesity (Trinh & Boulianne, 2013), there are few comparative studies on obese phenotypes produced by food. Prior research indicates that *Drosophila melanogaster* living under a PRD live longer (Regan *et al*., 2016). Moreover, PRD has been linked to higher locomotor activity in *Drosophila*, lower stress resistance, and increased expression of antioxidant genes (Sun *et al*., 2012). PRD correlated with increased fat reserves in *Drosophila melanogaster* larvae in adult flies because of elevated gene expression associated with fat mobilization and droplets of lipid storage in adult flies (Rehman & Varghese, 2021). There are still several difficulties in utilizing *Drosophila melanogaster* to represent obesity diseaseDespite the fact that *Drosophila melanogaster* is a highly accurate model of obesity, (Trinh & Boulianne, 2013), there are few comparative studies on obese phenotypes produced by food. There are still several difficulties in utilizing *Drosophila* melanogasterto represent obesity diseaseThe adoption of the High Sugar Diet to mimic obesity has been related to hyperosmolarity and glucotoxicity in flies (Na *et al*., 2015; Rovenko *et al*., 2015). Yet, the use of a high-fat diet has been connected to lipotoxicity, which triggers inflammatory processes that endanger signaling networks within cells (Hong *et al*., 2016). This effort aimed to make a diet-induced fly obesity model more reliable and healthier by reducing its number of variables. Thus, the purpose of this study was to examine the effects of three distinct diets on the survival, mass, total protein, sterol and triglyceride content, total protein, and catalase activity of obese *Drosophila melanogaster* larvae and adults. The diets included high fat, high sugar, and protein restriction.

Impact of high stravation diet in *Drosophila melanogaster*

Starved *Drosophila melanogaster* larvae exhibit carnivorous behaviour

Recent research has demonstrated that when the melanogaster *Drosophila melanogaster* larvae are under nutritional stress, they can successfully metamorphose into predators and subsist consuming larger

conspecifics as food in a cannibalistic manner (Vijendravarma *et al*., 2013). Our objective was to assess the degree of starvation-induced carnivorous behavior in because *Drosophila melanogaster* larvae do not eat carnivorous foods; they are generally classified as herbivores. To track the larvae's propensity for cannibalism, they were raised only on whole, conspecific adult carcasses. *Drosophila melanogaster* red eye pigment accumulated in the larval intestine as a result of consuming adult corpses. This data aligns nicely with previous research that indicated *Drosophila hydei* larvae can consume adult carcasses of the same species (Gregg *et al*., 1990). Following the discovery of cannibalism caused by malnutrition in *Drosophila melanogaster* larvae, further investigated the possibility of starving larvae consuming carcasses belonging to different taxonomic groups. For the purpose of this study, Larvae were cultivated exclusively on decontaminated carcasses of *Araneae sp., Musca domestica*, and *Apis mellifera*. Larvae gathered the adult carcasses in each case and ate them. It was possible to evaluate the preferred diet of well-fed larvae by presenting the *Musca domestica* carcass and cornmeal medium simultaneously. After 30 minutes of exposure to the carcass and cornmeal medium, there was a noticeable amount of larvae aggregation around the medium as opposed to the carcass.

Starved larvae scavenge conspecific larval carcasses

It has been observed that younger *Drosophila melanogaster* larvae consume live wandering-stage conspecific larva (Vijendravarma *et al*., 2013). Stain-treated larval carcasses were given to the hungry larvae in order to assess their capacity for scavenging conspecific larval carcasses. The accumulation of green dye in the larval stomach indicates that, similar to how they absorbed dyed eggs, starving larvae also consumed stained conspecific larval carcasses. Larval carcasses were stained with two distinct dye colors (red and green), and then they were offered to starving larvae beside a piece of agar with a separate color. On the same petri plate, one hundred starving larvae were given the option of red-colored larval carcasses or green agar. After switching the colors, another batch of 100 starving larvae was given the identical option. Significant larval aggregation was seen for each trial after 30 minutes, suggesting that the nutritional content of the dead conspecifics was devoured by famished larvae and that the color of the dye had no effect on the larvae's intake of their corpses.

Adult *Drosophila melanogaster* also display cannibalistic behaviour when they are starved

The adult flies could also feed on the carcasses of *Drosophila melanogaster* larvae when they were starving because of the cannibalistic behavior of *Drosophila melanogaster* larvae towards dead larvae. In order to ascertain the existence of this type of cannibalism in adult *Drosophila*, entire, sterilized third-instar larval carcasses were fed to famished flies. Interestingly, these famished adult flies perished in less than a day without eating the corpses of their conspecific larvae. This finding is consistent with a prior study in which adult carcasses were provided to famished flies, but no signs of cannibalism were noted (HUEY *et al*., 2004). This may be because adult *Drosophila melanogaster* do not have the necessary physical features to puncture conspecifics' cuticles (Spencer, 1953). During the same experiment, it's important to note that female adult flies were shown to oviposit primarily on and around the dead carcasses of conspecific third instar larvae. To further understand this behaviour, two sets of larval carcasses coated with Para film or left nude were shown by flies. Compared to the carcasses wrapped with Para film, a notably higher quantity of eggs was laid around the nude larvae. It is commonly known that *Drosophila melanogaster* egg laying is directly correlated with food availability (Terashima & Bownes, 2004), and that females prefer to lay their eggs close to nutritional substrates (Miller *et al*., 2011). Our findings indicate that adult flies favourably deposited their eggs on and around bare larval remains, despite the fact that they are incapable of consuming complete larval carcasses.

Molecular mechanism of aging signaling pathway and circadian clock dependent metabolic pathway

Nutrient signalling in yeast enables colonies physiology and co-ordinate cell division in response to external stimuli. When nutrients are few, 90–99% of the colony dies of natural causes (Fabrizio *et al*., 2004), leaving the remains of the colony to endure on the limited nutrients. This contributes to the accomplishment of a clonal population's main goal, which is to maximize future replication of its shared genome, by ensuring that a small number of individuals will survive the harsh environmental conditions. A group of tissues in multicellular creatures have unique nutrition sensing abilities. For instance, in *C. elegans*, the gonad, the colon, and neurons are the main sites of nutrition signalling. Insulin/insulin-like growth factor (IIS) and target of rapamycin (TOR), which are both known to modify longevity, are the key nutritional signalling pathways, just like in higher animals (Lapierre & Hansen, 2012; Panowski & Dillin, 2009). In neurons, the insulin receptor binds insulin-like peptides that are produced in response to nutritional sensing. By communicating with the colon and gonads, loss of DAF-2, the worm's sole insulin/IGF-1-like receptor, lengthens worm life (Libina *et al*., 2003). Longevity is also aided by germline loss, which enhances autophagy and releases stored fat in the gut (Lapierre *et al*., 2011; Wang *et al*., 2008). Lastly, prolonging life and simulating the effects of calorie restriction are achieved by decreasing TOR activity (Kapahi *et al*., 2010). Combined, these findings demonstrate that *C. elegans* aging and lifespan are influenced by changes in nutrition signalling during development and reproduction. Coordinating growth and reproduction with the environment through long-range signals, mostly insulin, allows the body to store and use energy efficiently. Similar to *C. elegans*, IIS signalling is integrated to the TOR pathway in *Drosophila melanogaster* and mammals via AKT/PI3K to facilitate growth and proliferation (Laplante & Sabatini, 2009; Niccoli & Partridge, 2012; Partridge *et al*., 2011). Delays in development and smaller, less fertile flies with longer lifespans are caused by inhibition of the TOR or IIS pathways in *Drosophila melanogaster* (Kapahi *et al*., 2010; Partridge *et al*., 2011). Aging-related traits do not arise as quickly in adult flies when similar treatments are applied (Kapahi *et al*., 2010; Partridge *et al*., 2011). Moreover, animals deficient in ribosomal S6 protein kinase 1 (S6K1), a downstream element of the TOR system, boast an extended lifetime and demonstrate resilience against age-related illnesses (Bjedov & Partridge, 2011; Shima, 1998; Um *et al*., 2004; Zhang *et al*., 2011). Giving rapamycin to worms, flies, or mice prolongs their lives by decreasing TOR signalling (Bjedov & Partridge, 2011). Mice that have reduced levels of the anabolic hormones insulin, growth hormone or IGF-1 live longer and are less susceptible to age-related disease (Brown-Borg & Bartke, 2012; Vinciguerra *et al*., 2012). Reduced plasma IGF-1-producing mutant mice exhibit a shorter lifespan (Panici *et al*., 2010)and a lower stature. Similarly, animals lacking the insulin receptor substrate 1 are long-lived but exhibit reduced insulin sensitivity (Selman *et al*., 2008). A hallmark of longer lifespans in humans is greater insulin sensitivity, which is demonstrated by lower levels of plasma insulin, IGF-1, and glucose (Barzilai *et al*., 2012). In fact, those lacking the GH receptor and suffering from Laron syndrome exhibit a notable decrease in pro-aging signaling, cancer, and diabetes (Guevara-Aguirre *et al*., 2011).

Mechanisms of the circadian clock and nutrition metabolism

The majority of species are subject to periodicity due to the yearly cycle around the Sun and the every day the Earth rotates around its axis. Molecular circadian clocks may have developed to best time activities like feeding, mating, and general patterns of activity by co-ordinating internal metabolic rhythms to dependable environmental cycles 38. Furthermore, an increasing amount of data points implies a mutual connection between the circadian rhythm and the nutrition sensing pathway *(Peek et al*., 2012).

Circadian signaling in worms

Compared to flies and mammals, *C. elegans* appears to employ a distinct mechanism to create daily cycles (Banerjee *et al*., 2005; Temmerman *et al*., 2011;

van der Linden *et al*., 2010). Despite the fact that the majority of fundamental circadian genes are preserved in *C. elegans* (Hasegawa *et al*., 2005; Temmerman *et al*., 2011) these genes are not known to express periodically in maturity (van der Linden *et al*., 2010) and instead often serve to time the periodic moults that occur during nematode larval development (Banerjee *et al*., 2005; Tennessen *et al*., 2006). These species do, however, exhibit observable regular cycles of circadian that are tied down by warm/cool or light or dark cycles. In terms of traits like motility (Saigusa *et al*., 2002; Simonetta *et al*., 2009) stress-resistance (Kippert *et al*., 2002; Simonetta *et al*., 2008), pathogen-resistance (Romanowski *et al*., 2011), food and oxygen consumption (Migliori *et al*., 2011), and gene expression (van der Linden *et al*., 2010), this rhythmicity can be measured in both larvae and adults. Moreover, the circadian process in *C. elegans* involves conserved signaling components. First, research has shown that *C. elegans* contributes to circadian rhythmicity during movement (Janssen *et al*., 2009). This is due to the action of pigment dispersion factor (PDF) and its receptor, which in insects, similarly to mammalian VIP (vasoactive intestinal peptide), translates circadian oscillations to downstream activities (Duvall & Taghert, 2012; Loh *et al*., 2011). Second, although its functional characterization is still pending, it has been recently discovered that melatonin and its synthase undergo circadian cycling (Migliori *et al*., 2012). Profiling genes that are rhythmically expressed during and after a 12-hour light cycle is carried out further downstream. Warm or cool cycles, in particular, revealed GO keywords associated with a wide range of biological processes, primarily metabolic processes, that have a higher concentration of genes that are responsive to changes in temperature or can be activated (van der Linden *et al*., 2010) . Notably, this study discovered that, in contrast to *Drosophila*, for instance, cycling of light and temperature entrained unique groups of genes. The discovery suggests that there could be multiple distinct clock systems or distinct gene tagging effects resulting from external stimuli.

Circadian signalling in flies

Compared to *C. elegans*, humans and *Drosophila melanogaster* appear to share most circadian clock genes and mechanisms. The transcriptional and translational feedback loops that make up the circadian clocks of flies and mammals function independently of individual cells. The four clock genes Clock, cycle, timeless , and period form the basis of the *Drosophila melanogaster* circadian clock. Cyc is an ortholog of BMAL1 in mammals (Hardin, 2011). They work in a negative feedback loop to regulate the expression levels of per and tim by interacting with transcriptional activators encoded by Clk and Cyc. The accumulation of PER and TIM protein in cell nuclei and their blockade of CLK/CYC activators leads to a periodic increase in these protein levels, which in turn inhibits the transcription of PER and TIM (Hardin, 2011). CLK/CYC heterodimers activate a large variety of clock output genes (Abruzzi *et al*., 2011; Hardin, 2011) as well as genes involved in secondary clock feedback loops, in addition to per and tim. Comparable to the suprachiasmatic nucleus (SCN) in mammals, the about 150 central pacemaker neurons (CPNs) that make up the fly central clock regulate rhythms of activity and rest (Taghert & Shafer, 2006).

Moreover, peripheral clocks are present in the majority of fly cells and include cells that oscillate in the excretory system, glia, fat, and sensory neurons are distinct to a certain tissue and not dependent on the central nervous system (Allada & Chung, 2010). Among them rhythmic clock output genes in both peripheral and central clock cells; examples include the enzymes that are involved in the production of glutathione (Beaver *et al*., 2012).

CONCLUSION

This review accomplishes that dietary stress induces substantial alterations in *Drosophila melanogaster* circadian gene expression. High fat and high sugar diets disrupt metabolic pathways and circadian rhythms, contributing to metabolic disorders and obesity. High alcohol diets impair liver function and metabolic regulation, while high protein diets and starvation impact energy balance and aging processes. The findings emphasize the complex interplay between diet, circadian gene expression, and metabolic health. Understanding these interactions can inform strategies to mitigate the

adverse effects of dietary stress on circadian rhythms and metabolic health, potentially leading to interventions that promote healthier aging. The review highlights the need for further research to elucidate the detailed molecular mechanisms underlying these effects and to explore potential therapeutic approaches for maintaining circadian and metabolic homeostasis under dietary stress conditions.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

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