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Photoperiod-dependent effects of (poly)phenol-rich extracts from seasonal fruits on the serum metabolome

Alberto Domingo-Gómez [a], Francesca Manocchio [a,b,1], Diego Morales [a,b,2], Anna Arola-Arnal [a,b,c], Francisca Isabel Bravo [a,b,c,*], Begoña Muguerza [a,c,d,*], Josep M. del Bas [a,b,c]

[a] Universitat Rovira i Virgili, Biochemistry and Biotechnology Department, Nutrigenomics Research Group, Tarragona 43007, Spain
[b] Nutrigenomics Research Group, Institut d'Investigació Sanitària Pere Virgili, C/ Marcel·lí Domingo s/n, 43007 Tarragona, Spain
[c] Center of Environmental, Food and Toxicological Technology (TecnATox), University Rovira i Virgili, C/ Marcel·lí Domingo s/n, 43007 Tarragona, Spain
[d] CIBERobn Physiopathology of Obesity and Nutrition, Institute of Health Carlos III, Madrid, Spain

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ABSTRACT

Seasonal rhythms are a recognised environmental factor affecting metabolism and health. In turn, phenolic compounds are recognised for their health-promoting properties and potential to influence biological rhythms. This work aimed to assess whether metabolic differences between seasons condition the response to dietary (poly)phenols. We exposed Fischer 344 male rats to short and long photoperiods simulating winter and summer, respectively. Eight different (poly)phenol-rich fruit extracts (FE) were administered, four obtained from spring-summer fruits and four of autumn-winter harvest fruits. A metabolomics-based approach was used for capturing systemic metabolic changes. Results showed a marked seasonal metabolic shift that conditions the response to FE. A common metabolic response to FE from autumn-winter fruits was identified accompanied by an anti-inflammatory pattern, suggesting that the effects were driven by shared seasonal characteristics of fruits rather than by the specific FE. Overall, (poly)phenols of seasonal fruits exert differential effects depending on the seasonally-conditioned metabolic state.

1. Introduction

Ecosystems are governed by perpetual change. Over time, organisms adapt to these fluctuations, enhancing their functional performance and survival. This process begins with the perception of environmental cues and culminates in corresponding physiological, behavioural, and/or morphological adjustments (Ebling, 2020). Some environmental factors (such as photoperiod, temperature, or humidity) exhibit oscillatory patterns throughout the year. Most species have evolved the ability to internalize these signals through time-measuring systems known as biological clocks. This molecular machinery orchestrates physiological reprogramming that generates biological rhythms, such as seasonal rhythms (Helm et al., 2013).

These physiological changes can impact human health. For instance, a more pro-inflammatory status occurs during the winter months in the northern hemisphere, characterized by increased circulating levels of

Abbreviations: AE, Apricot Extract; ANOVA, Analysis of Variance; BCAA, Branched chain amino acid; BW, Body weight; C, Control; CRP, C-reactive protein; ChE, Cherry Extract; ELISA, Enzyme-linked immunosorbent assay; FE, Fruit extracts; F344, Fischer 344; FDR, False discovery rate; GC-qTOF, Gas chromatography-quadrupole time of flight; GE, Grape Extract; IL-10, Interleukin-10; IL-6, Interleukin-6; KE, Kaki extract; L18, 18 h of light per day; L6, 6 h of light per day; LPS, Lipopolysaccharide; MCFA, Medium-chain fatty acid; OE, Orange Extract; OPLS, Orthogonal partial least square; PCA, Principal component analysis; PC, Principal component; PE, Plum Extract; PERMANOVA, Permutational multivariate analysis of variance; PmE, Pomegranate extract; PLS-DA, Partial least square-discriminant analysis; PxE, Photoperiod extract interaction; QEA, Quantitative enrichment analysis; SD, Short day; SE, Strawberry Extract; TCA, Tricarboxylic acid cycle; TNF-α, Tumour necrosis factor-α; VIP, Variable importance in projection.

* Corresponding authors at: Universitat Rovira i Virgili, Biochemistry and Biotechnology Department, Nutrigenomics Research Group, Tarragona 43007, Spain.
E-mail addresses: franciscaisabel.bravo@urv.cat (F.I. Bravo), begona.muguerza@urv.cat (B. Muguerza).
[1] Current affiliation: Universitat Pompeu Fabra, Medical and Life Science Department, PRBB BUILDING, 08003 Barcelona, Spain.
[2] Current affiliation: Departmental Section of Galenic Pharmacy and Food Technology, Veterinary Faculty, Avda. Puerta del Hierro s/n, Complutense University of Madrid, 28040, Madrid, Spain.

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interleukin-6 (IL-6) and C-reactive protein (CRP). These biomarkers are positively correlated with autoimmune, cardiovascular and psychiatric conditions (Dopico et al., 2015). Likewise, lipid metabolism undergoes seasonal variations, with elevated blood cholesterol and body fat mass typically observed during winter (Kanikowska et al., 2015). Consistently, blood pressure is higher in winter compared to summer, in line with an increased prevalence of metabolic syndrome during colder months (Grundy et al., 2005). Together, these variations suggest that human health is more vulnerable in winter (Kamezaki et al., 2013).

Similar seasonal patterns have also been reported in photoperiod-sensitive rodents. Exposure to short-day (SD) photoperiods has been associated with increased energy expenditure, with reduced body weight (BW), food intake and reproductive activity (Prendergast et al., 2004). From a systemic perspective, these animals also display a more pronounced catabolic state during winter (Navarro-Masip, Caron, et al., 2023).

One approach to mitigate health issues associated with seasonality is consuming certain phytochemicals, such as (poly)phenols. These are plant-derived compounds whose structure and concentration are shaped by environmental conditions, including temperature, light, stress, and day length (Jaakola & Hohtola, 2010). (Poly)phenols are well known for their antioxidant and anti-inflammatory properties, and evidence suggests they can interact with key signalling pathways in the organism, potentially modulating physiological responses (Beauchamp et al., 2005; Le Sage et al., 2017). Importantly, recent studies proposed that the effects of certain (poly)phenols on metabolism may be photoperiod dependent (Rodríguez et al., 2022). For instance, previous research has shown that (poly)phenol-rich fruit extracts, obtained from fruits harvested in different seasons, can modulate cholesterol and glucose blood levels in a photoperiod-dependent manner (Manocchio et al., 2024; Manocchio et al., 2025). Nevertheless, the underlying mechanisms remain unclear.

Considering this, we hypothesized that photoperiod-sensitive subjects display season-dependent physiological profiles that determine their metabolic responses to dietary phytochemicals. Elucidating how these season-dependent states respond to phytochemicals is essential for tailoring individualized dietary recommendations. Therefore, this study aimed to characterise the hallmarks of metabolic differences between seasons and their response to different (poly)phenol-rich extracts. Moreover, we sought to identify common metabolic responses to extracts from different fruits sharing harvesting season but differing in (poly)phenolic content. We used a photoperiod-controlled preclinical model, representative of two seasons, treated with extracts from eight fruits: four representatives of early- (spring-summer; cherry, plum, apricot, strawberry) and four of late- (autumn-winter; grape, orange, persimmon kaki and pomegranate) local harvest. A metabolomics- and machine learning-based approach was used for capturing systemic metabolic changes and generating insights into the pathways involved in the response (Wishart, 2016).

2. Methods

2.1. Seasonal-fruit extracts obtention and characterization

We classified the fruits in two groups according to their typical harvesting period: extracts from fruits typically harvested at spring-summer season included cherry (ChE, from *Prunus avium* L. var. *lapins*; Sierra el Frasno, Zaragoza, Spain), apricot (AE, from *Prunus armeniaca* L.), plum (PE, from *Prunus domestica* L. var. *black diamond*; Ruidoms, Tarragona, Spain) and strawberry (SE, from *Fragaria vesca* L. var. *cadonga*; Reus, Tarragona, Spain); while extracts from autumn-winter fruits included grape (GE, from *Vitis vinifera* L. var. *cabernet*; Constantí, Tarragona, Spain), persimmon kaki (KE, from *Diospyros kaki* L.f. var. *rojo brillante*; Ruidoms, Tarragona, Spain), orange (OE, from *Citrus sinensis* L. var. *navelina*; Cambrils, Tarragona, Spain) and pomegranate (PmE, from *Punica granatum* L. var. *tendral de valencia*; Benissanet, Tarragona, Spain). Fruit extracts (FE) were obtained as described by Francesca Manocchio et al. (Manocchio et al., 2024).

2.2. Animal experiment

In biorhythms research, strains such as Fischer 344 (F344) rats are considered suitable models for investigating seasonal adaptation (Heideman et al., 2000; Heideman & John, 1997; Ross et al., 2009; Shoemaker & Heideman, 2002; Tavolaro et al., 2015), and a $N = 8$ individuals per group is sufficient to obtain a significant difference in body weight between photoperiods differing in 8 h, which was set as the primary outcome (Tavolaro et al., 2015). Therefore, a total of 144 male 8 weeks-old F344 rats, with an approximated BW of 250 g, were purchased from Charles River Laboratories (L'Arblese, Cedex, France). Animals were maintained at 12 h light/dark cycle, 55% ± 15% of relative humidity and 22 ± 5 °C throughout the experiment, acclimated during 1 week, then randomly assigned to two groups ($n = 72$ per group with two animals per cage according to welfare protocols), each exposed to either L6 (6 h of light per day) or L18 photoperiod (18 h of light per day) for 4 weeks, simulating winter and summer seasons, respectively. Lights were turned on at 7:00 a.m. in both conditions. After 4 weeks of adaptation to the new photoperiod (Fig. 1a), diet was daily supplemented with 100 mg/Kg BW of one FE or 1.0 mL of water (control groups, L6-C and L18-C), for 2 weeks ($n = 8$ per group). The same extract batches were used for animals in both L6 (L6-GE, L6- OE, L6-PmE, L6-KE, L6-ChE, L6-PE, L6-SE and L6-AE) and L18 (L18-GE, L18-OE, L18-PmE, L18-KE, L18-ChE, L18-PE, L18-SE and L18-AE) photoperiods. Animals were randomly assigned to each group. Supplementation was performed by voluntarily liking a syringe between 8:00 and 9:00 a.m. After supplementation period, blood was collected from saphenous vein in non-heparinized tubes and centrifuged (3000 x*g* for 15 min at room temperature). The resultant serum was stored at −80 °C until processed for metabolite identification. After a 4-day wash-out, animals received two more weeks of supplementation before a lipopolysaccharide (LPS) challenge. Briefly, 3 h after treatment animals were administered a 0.5 mg/Kg BW dose of LPS intraperitoneally, and four hours after administration were sacrificed by decapitation. Blood samples processing and levels of IL-6, interleukin-10 (IL-10), tumour necrosis factor-α (TNF-α) and CRP, were determined as presented in Francesca Manocchio et al. (2025) (Manocchio et al., 2025). No animals were discarded after following the animal welfare supervision protocols during the experiment and no adverse effects were observed. Blinding was followed for allocation and conduction of the experiment and opened for further assessment. The animal Ethics Committee of the University Rovira i Virgili (Tarragona, Spain) and Generalitat de Catalunya (permission number 11,610) agreed to the animal procedures used in this study.

2.3. Metabolomic profiling

Serum samples were prepared by protein precipitation protocol as follows: eight volumes of methanol:water (8:2, v/v), containing a mixture of internal standards, were added to each sample to precipitate proteins and extract metabolites. Then, samples were mixed and incubated at 4 °C for 10 min, centrifuged at 15,000 rpm, and the resulting supernatant was evaporated to dryness prior to compound derivatization (methoximation and silylation). The derivatized compounds were analysed by gas chromatography coupled to quadrupole time-of-flight mass spectrometry (GC-qTOF, model 7200 of Agilent, USA).

Internal standards were succinic acid (D4, 98%), myristic acid (D27, 98%), norvaline, adonitrol, glycerol (13C3, 99%), D-glucose (13C6, 99%), provided by Sigma Aldrich. Acetic-2,2-acid (D6, 98%) was purchased from CDN Isotopes (Leacock, Canada). Alpha-ketoglutaric acid (D6, 98%) and the metabolomics amino acid mix standard containing glycine (13C2, 99%; 15N, 99%), L-Alanine (13C3, 99%; 15N, 99%), L-Arginine·HCl (13C6, 99%; 15N4, 99%), L-Aspartic Acid (13C4, 99%; 15N, 99%), L-Cystine (13C6, 99%; 15N2, 99%), L-Glutamic Acid (13C5,

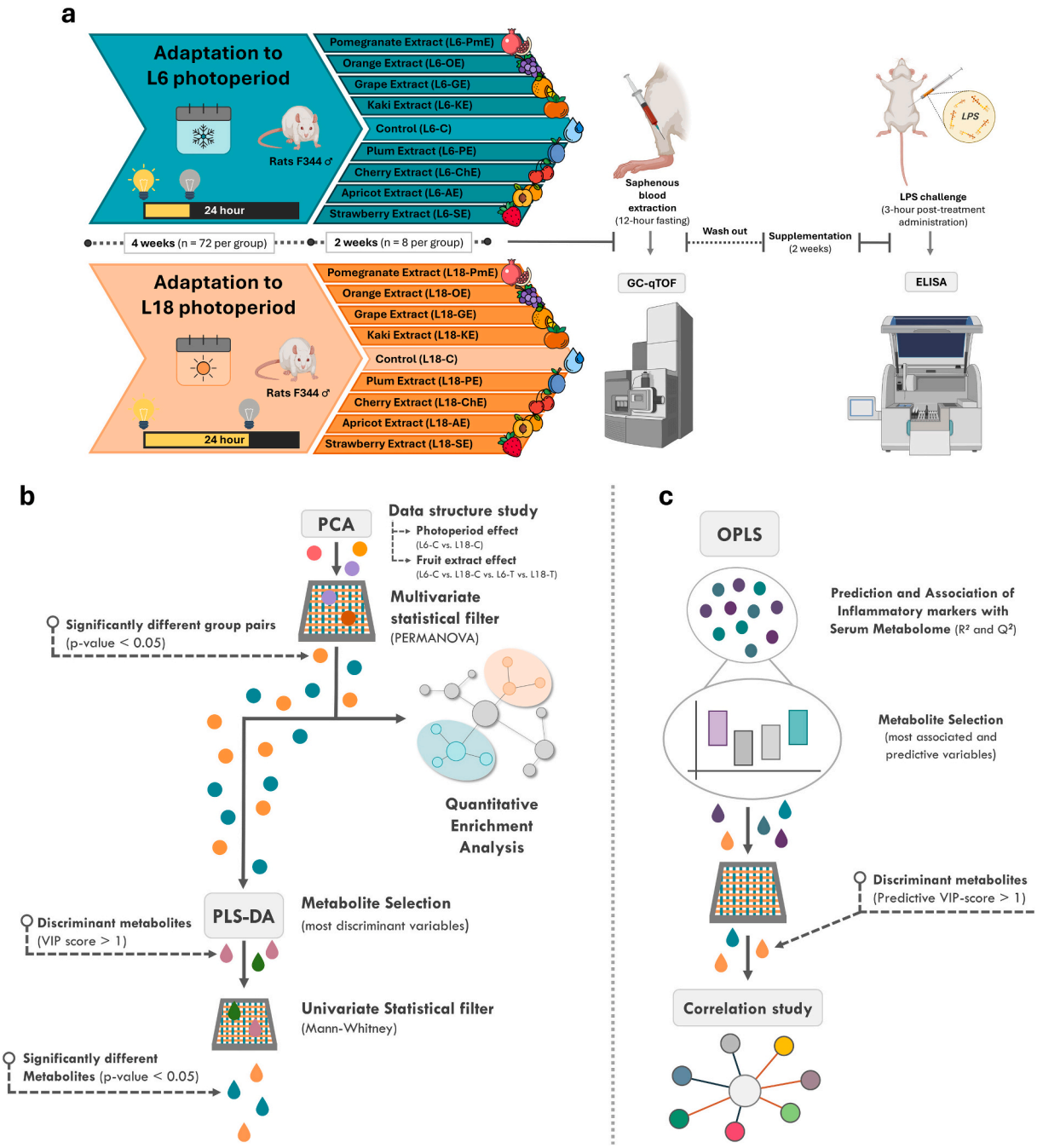


Fig. 1. Schematic overview of the animal study and the statistical analyses. (a) Animal experiment workflow and sample collection. (b) Multivariate approach to evaluate the effects of photoperiod and fruit extracts on the serum metabolome. (c) Assessment of predictive and associative features between serum metabolites and inflammatory markers following the LPS challenge and correlation study of the inflammatory markers and the most associated metabolites. AE = apricot extract, ChE = cherry extract, ELISA = enzyme-linked immunosorbent assay, F344 = Fischer 344, GC-qTOF = gas chromatography-quadrupole time-of-flight mass spectrometry, GE = grape extract, KE = kiwi extract, L18 = 18 h of light per day, L6 = 6 h of light per day, LPS = lipopolysaccharide, OE = orange extract, OPLS = orthogonal partial least squares, PCA = principal component analysis, PE = plum extract, PERMANOVA = permutational multivariate analysis of variance, PLS-DA = partial least squares-discriminant analysis, PmE = pomegranate extract, SE = strawberry extract, VIP = variable importance projection.

99%; 15N, 99%), L-Histidine·HCl·H2O (13C6, 97–99%; 15N3, 97–99%), L-Isoleucine (13C6, 99%; 15N, 99%), L-Leucine (13C6, 99%; 15N, 99%), L-Lysine·2HCl 134 (13C6, 99%; 15N2, 99%), L-Methionine (13C5, 99%; 15N, 99%), L-Phenylalanine (13C9, 99%; 15N, 99%), L-Proline (13C5, 99%; 15N, 99%), L-Serine (13C3, 99%; 15N, 99%), L-Threonine (13C4, 97–99%; 15N, 97–99%), L-Tyrosine (13C9, 99%; 15N, 99%), L-Valine (13C5, 99%; 15N, 99%) were obtained from Cambridge Isotope Laboratories. All reagents were analytical grade.

The chromatographic separation was based on Flehn Method, using a J&WSccientific HP5-MS (30 m x 0.25 mm i.d., 0.25 mm film capillary column and helium as carrier gas using an oven program from 60 to 325 °C). Ionization was done by electronic impact (70 eV, full scan mode). Identification of metabolites was performed using commercial standards listed above, and by matching their EI mass spectrum and retention time to metabolomic Fiehn library (Agilent) which contains more than 1400 metabolites. After putative identification of metabolites, these were semi-quantified in terms of internal standard response ratio. Assessed metabolites are shown in Supplementary Table 1.

2.4. Statistical analysis

All analyses were performed using R version 4.5.1 (R Core Team, 2025). The analysis followed the workflow exposed in Fig. 1b and c. Data is available under reasonable request.

2.4.1. ANOVA

An Analysis of Variance (ANOVA) was conducted to evaluate the effects of photoperiod and FE on BW and food intake. Post hoc comparisons were performed using Tukey's test. Differences were considered statistically significant at $p < 0.05$. All analyses were conducted using the base stats package in R (R Core Team, 2025).

2.4.2. Principal component analysis

Principal Component Analysis (PCA) was employed to explore the underlying structure of the data. Specifically, PCA was used to assess the effect of photoperiod by comparing the control groups (L6-C and L18-C), and to evaluate the impact of FE consumption by analysing the relative data distribution among L6-C, L18-C and the two groups treated with the same fruit extract. Serum metabolome was used as input data, standardizing all variables using autoscaling procedure. This method was performed in R using mixOmics R package (Rohart et al., 2017). Results were plotted using ggplot2 R package (Hadley, 2009).

2.4.3. PERMANOVA

Permutational Multivariate Analysis of Variance (PERMANOVA) was used at a multivariate and univariate level to assess the effects of fruit extract administration, photoperiod, and their interaction on the serum metabolome. It also served to evaluate differences between groups. In both univariate and multivariate approaches, a total of 1000 permutations were performed to determine statistical significance, and post-hoc comparisons were adjusted using the Benjamini-Hochberg correction. Adjusted *p*-values below 0.05 were considered statistically significant. This method was performed using PERMANOVA R package (Laura Vicente-Gonzalez, 2021).

2.4.4. Partial least squares-discriminant analysis

Partial Least Squares-Discriminant Analysis (PLS-DA) was applied to examine the photoperiod effect by comparing both control groups, as well as to study the treatment effect by comparing each treated group with its respective control under the same photoperiod. Specifically, we examined the variable importance in projection (VIP) scores derived from these PLS-DA, which in this case indicate the discriminative power of each metabolite in each group comparison. A VIP score threshold of 1 was applied, with metabolites having a VIP score greater than 1 considered as the most discriminant metabolites (Zheng et al., 2023). To ensure the quality of the models, R^2x cumulative values were extracted, and balanced error rate (BER) was computed via M-fold cross validation (5 folds and 10 repetitions). Models yielding a final cross-validated BER below 0.10 were classified as having excellent predictive quality, those between 0.10 and 0.20 were considered acceptable, and BER values above 0.20 were classified as weak (Supplementary Fig. 1). PLS-DA method was performed in R using mixOmics package, and the results were plotted using ggplot2 package (Hadley, 2009; Rohart et al., 2017).

2.4.5. Quantitative enrichment analysis

The quantitative enrichment analysis (QEA) was used to determine which metabolic pathways were significantly altered in response to photoperiod changes, by comparing both control groups. Besides, QEA allowed to identify altered pathway due to FE consumption by comparing each treated group with the respective control group under the same photoperiod. Pathways with a *p*-value and false discovery ratio (FDR) lower than 0.05 were considered statistically significant. This analysis and plots were performed using MetaboAnalystR and ggplot2 R packages, respectively (Hadley, 2009; Pang et al., 2020).

2.4.6. Orthogonal partial least square

Orthogonal Partial Least Squares (OPLS) was employed to evaluate the association between serum metabolome data and blood inflammatory markers obtained after the LPS challenge (IL-6, IL-10, TNF-α and CRP), used as predictor and response variables, respectively. Additionally, it allowed us to identify key metabolites driving the variation in, and correlating with, the response variables. This method was performed and plotted using ropls and ggplot2 R packages (respectively) (Hadley, 2009; Thévenot et al., 2015).

2.4.7. Spearman correlation

Spearman correlation was used to evaluate the relationships between CRP, IL-10, and serum metabolites. Analyses were performed using the base stats package in R (R Core Team, 2025).

3. Results

3.1. Effects of the photoperiod

Two-way ANOVA showed that rats exposed to L6 had lower (BW) compared with those under L18 within the same treatment ($p < 0.05$). Food intake was not changed FE treatments nor by photoperiod (Table 1).

Differential effects of the photoperiod in the metabolome of control animals (i.e. L6-C and L18-C) were assessed (Supplementary Table 1). PCA revealed a clear separation between both groups along the principal component (PC) 1, which explains 38.31% of the total variance (Fig. 2a). This suggested that their metabolomic profiles were markedly distinct. PERMANOVA test indicated significant differences (adjusted *p*-value <0.01) (Supplementary Table 2).

The contribution of each metabolite to group separation was assessed using PERMANOVA and the VIP score derived from PLS-DA regression, with metabolites showing p-value <0.05 and VIP score > 1 considered as the most discriminant variables (Supplementary Tables 3, 4, 5). These were predominantly enriched in branched chain amino acids (BCAAs); medium-chain fatty acids (MCFAs); and tricarboxylic acid cycle (TCA) intermediates (Fig. 2b). Notably, BCAAs, MCFAs (except dodecanoic acid) and succinic acid were significantly higher in L6-C respect to L18-C (Fig. 2c). Thus, we observed increased levels ranging from 10% to 20%, 10% to 40% and 30% for BCAAs, MCFAs and succinic acid, respectively (Supplementary Table 6).

Table 1
Final body weight and food intake of F344 rats exposed to L6 and L18 photoperiods for 6 weeks and administered water (control) or extracts (100 mg/Kg BW) the last two weeks.

Experimental groups	Body weight[1]		Food intake[2]	
	L6	L18	L6	L18
C	318.9 ± 18.9	333.8 ± 13.6	16.2 ± 0.6	17.4 ± 1.3
ChE	317.1 ± 16.3	344.9 ± 11.1	17.2 ± 1.2	18.7 ± 1.8
PE	315.5 ± 19.2	333.2 ± 19.8	16.4 ± 1.3	18.4 ± 1.8
AE	312.9 ± 14.5	339.2 ± 24.5	17.2 ± 1.1	16.9 ± 0.7
SE	312.0 ± 15.7	337.1 ± 23.1	17.3 ± 1.7	18.8 ± 1.2
KE	312.6 ± 25.5	336.6. ± 13.9	17.2 ± 1.1	17.3 ± 1.7
GE	310.1 ± 14.3	350.4 ± 22.9	16.9 ± 0.7	19.0 ± 1.3
OE	320.5 ± 21.6	338.5 ± 11.9	17.5 ± 2.0	18.0 ± 0.3
PmE	320.5 ± 14.7	346.5 ± 25.9	17.9 ± 1.9	18.8 ± 1.7

Values are expressed as mean ± standard deviation ($n = 8$ per group). A 2-way ANOVA was conducted comparing controls with each extract, separately, at both photoperiods (L6, L18). [1] For body weight, the two-way ANOVA revealed a significant effect of the photoperiod factor ($p < 0.05$), but no effect of the experimental group or the interaction. [2] For food intake, the two-way ANOVA showed no significant effects for any factor or their interaction. AE = apricot extract, ANOVA = Analysis of Variance, BW = Body weight, ChE = cherry extract, C = control group, GE = grape extract, KE = kaki extract, L18 = 18 h of light per day, L6 = 6 h of light per day, OE = orange extract, PE = plum extract, PmE = pomegranate extract, SE = strawberry extract.

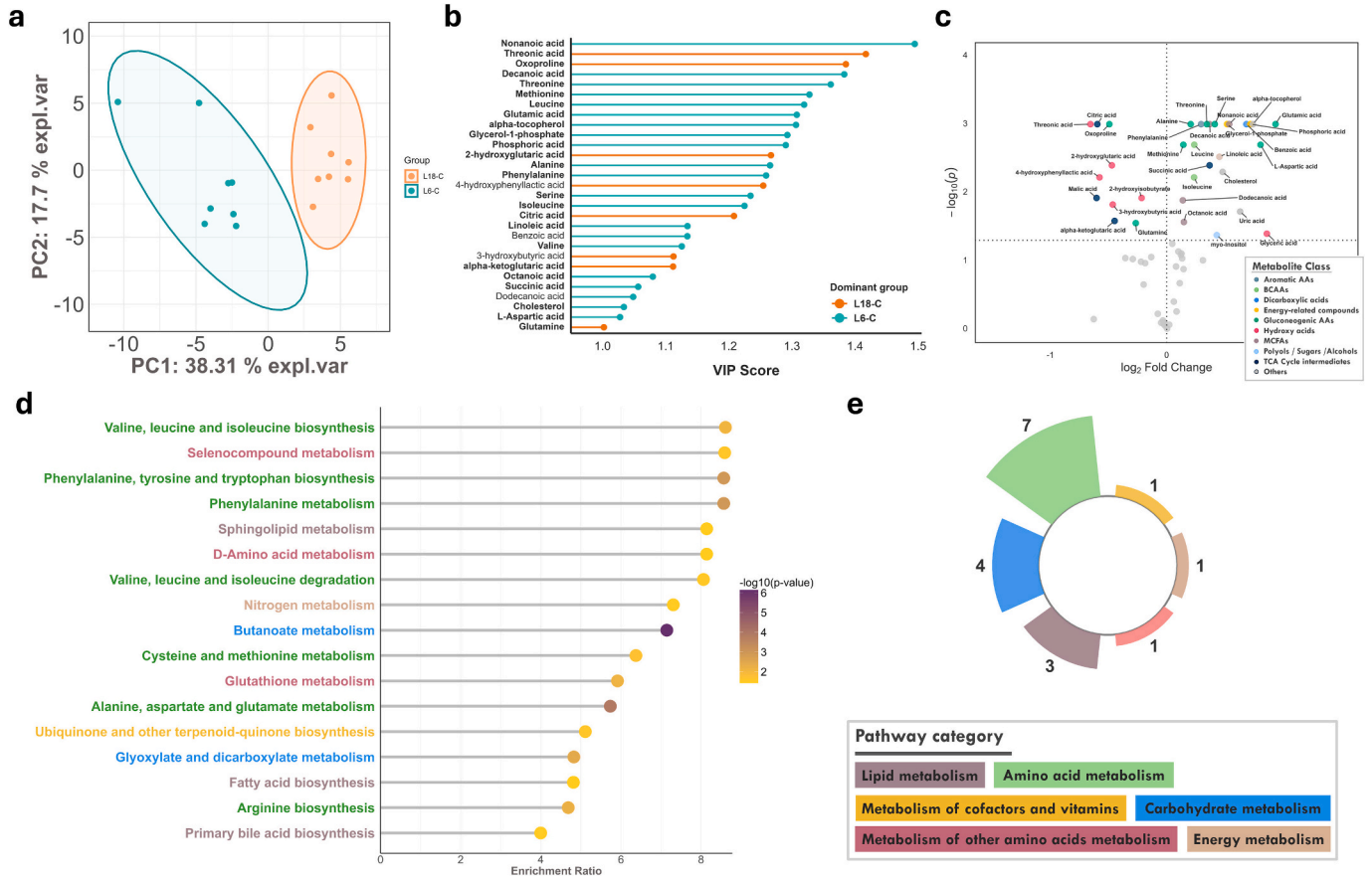


Fig. 2. Impact of photoperiod on the serum metabolome. (a) PCA scores plot of control groups under different photoperiod conditions along the PC1 and PC2. A significant photoperiod effect was confirmed by PERMANOVA (*p*-value adj. shown). (b) Lollipop plot showing the VIP scores obtained from PLS-DA analysis. Metabolites with VIP score > 1 are displayed, highlighting those that are significantly different between control groups (p-value <0.05). Colours indicate the group in which each metabolite is more abundant. (c) Volcano plot depicting photoperiod-related differences in serum metabolites concentrations. Each point is coloured by metabolite class, reflecting both statistical significance (y-axis) and magnitude of change (x-axis). (d) Bubble plot from QEA, comparing the number of significantly altered pathways (FDR < 0.05) across different KEGG pathway categories, based on BRITE hierarchy. The enrichment ratio is plotted on the x-axis, while bubble colour indicates the p-value. (e) Radar plot summarizing QEA results, showing the number of significantly altered pathways (FDR < 0.05) per functional category, based on BRITE hierarchy classification. Bar size represents the number of pathways affected, and colours denote pathway categories. The numbers represent the quantity of altered pathways for that size. AAs = amino acids, BCAAs = branched chain amino acids, C = control, FC = fold change, FDR = false discovery ratio, L6 = 6 h of light 6, L18 = 18 h of light, MCFAs = medium-chain fatty acids, PCA = principal component analysis, PERMANOVA = permutational analysis of variance, p = p-value, PLS-DA = partial least square-discriminant analysis, QEA = quantitative enrichment analysis, TCA = tricarboxylic citric acid, VIP = variable importance projection.

Regarding the alterations in specific metabolic pathways, the QEA procedure revealed that most significantly altered pathways belonged to energy, lipid, amino acid and amino acid derivates metabolisms (Fig. 2d, e and Supplementary Table 7). These metabolic routes include most of the aforementioned discriminant metabolites, suggesting a coordinated alteration of its metabolic context.

3.2. *Effect of consumption of autumn-winter fruit extracts*

To assess the differential metabolic effects of photoperiod and autumn-winter FE consumption, we analysed the metabolomes of control and treated animals (Supplementary Tables 8, 9). For each extract, a PCA was performed comparing the two control groups against the two respective treated groups. No effects of animal cage grouping were detected and therefore this variable was not identified as confounder. Consumption of GE and OE induced a clustering overlap with L6-C, clearly separating them from L18-C (Fig. 3a, b), suggesting that GE and OE consumption result in a metabolomic profile similar to that of the L6-C group. PmE groups did not overlap but clustered together along PC2, describing a major similarity between them (Fig. 3c). Similarly, KE, triggered the colocalization of both treated groups, being remarkably alienated with L6-C at the PC1 (Fig. 3d).

Subsequent PERMANOVA test revealed that both extract type and photoperiod induced significant alterations in all cases (Supplementary Table 2). A significant interaction between extract type and photoperiod was observed for GE, OE and PmE, but not for KE. These results suggest that the metabolic effects of GE, OE, and PmE are shaped by the photoperiod under which they are consumed (as indicated by the significant interaction), whereas KE impact appears to be independent of photoperiod conditions (Supplementary Table 9). Also, all treated groups were significantly different respect the control group under the same photoperiod (Supplementary Table 2).

To explore differences at the individual-metabolite level, we constructed a set of key discriminant metabolites for each treatment-control comparison using the same conditions as before: VIP score > 1 and *p*-value < 0.05, obtained from PLS-DA and PERMANOVA, respectively (Fig. 3e and Supplementary Tables 11, 12, 13, 14, 15, 16). At L18, these metabolite sets overlapped considerably among GE, OE and KE, and were enriched in several BCAAs, presenting an increase of the 5–10%. In contrast, while PmE presented a similar metabolite set, the overlap with other FE was less pronounced. Under the L6 photoperiod, the metabolite sets were smaller and predominantly enriched in MCFAs. Specifically,

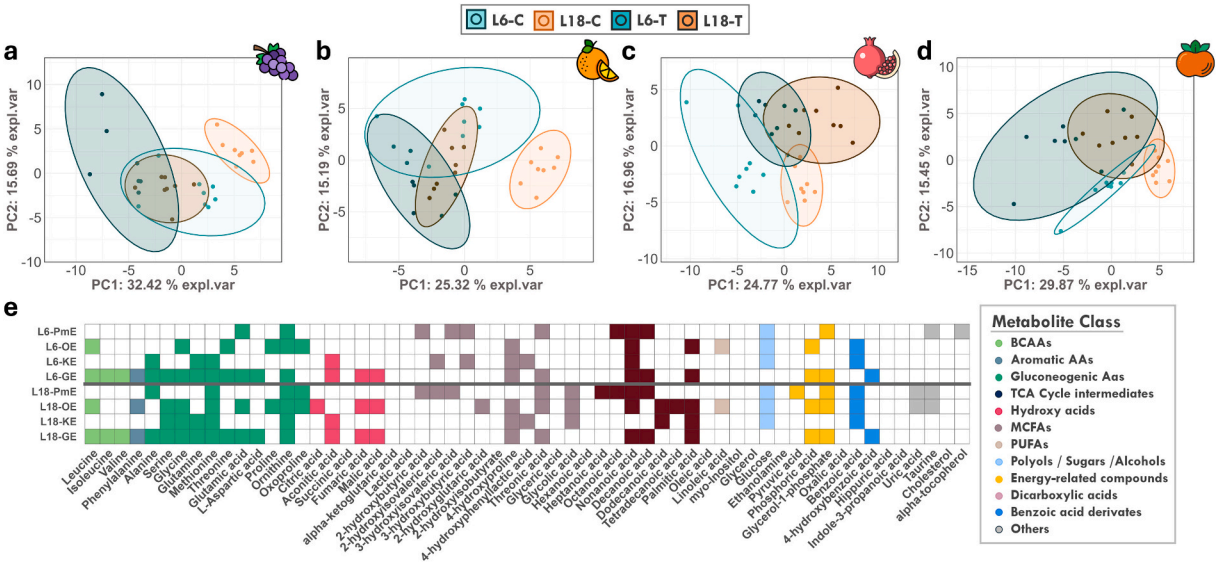


Fig. 3. Effects of autumn-winter fruit extracts on serum metabolome structure and identification of key discriminant metabolites. PCA plots for GE (a), OE (b), PmE (c), and KE (d) extracts under different photoperiod conditions. (e) Tile plot displaying key discriminant metabolites for each treated group compared to their corresponding photoperiod-matched control. Only metabolites with a PLS-DA derived VIP score > 1 and p-value <0.05 are coloured. Colour indicates the metabolite class. AAs = amino acids, BCAAs = branched chain amino acids, C = control, GE = grape extract, KE = kaki extract, L6 = 6 h of light, L18 = 18 h of light, MCFAs = medium-chain fatty acids, OE = orange extract, PCA = principal component analysis, PLS-DA = partial least square-discriminant analysis, PmE = pomegranate extract, PUFAs = polyunsaturated fatty acids, T = treated, TCA = tricarboxylic citric acid, VIP = variable importance projection.

there was a considerable reduction in certain MCFAs species following GE, OE and PmE administration (Supplementary Tables 17, 18). Lastly, in all groups, independent of the photoperiod, there was a consistent increase in hydroxy acid species.

Afterwards, we performed a QEA comparing each treated group to its respective control group under the same photoperiod (Supplementary

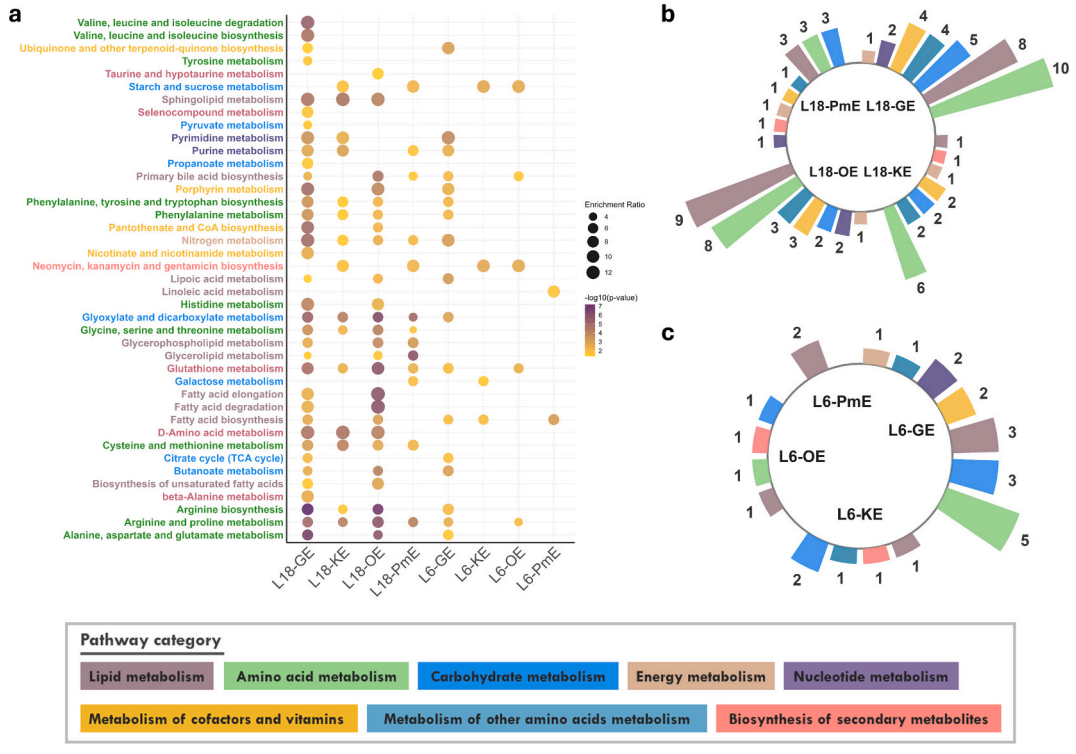


Fig. 4. Quantitative Enrichment Analysis of autumn-winter fruit extract administration under different photoperiods. Significantly altered pathways (FDR < 0.05) are showed. KEGG was used as the reference database. (a) Bubble plot illustrates the distribution of significantly enriched metabolic pathways for L18 and L6 photoperiod conditions, following autumn-winter extract administration. Each bubble represents a pathway coloured according to the BRITE hierarchy pathway category. The size of the bubble indicates the enrichment ratio, while the colour reflects the statistical significance of the alteration. Radar plots represent the number of significantly altered pathways within each pathway category for L18 (b) and L6 (c) photoperiods. The length of the bars denotes the number of altered pathways, and the colours correspond to BRITE-classified pathway categories. FDR = false discovery rate, GE = grape extract, KE = kaki extract, L6 = 6 h of light, L18 = 18 h of light, OE = orange extract, PmE = pomegranate extract.

Tables 19, 20, 21, 22, 23, 24, 25, 26). This analysis showed that, at both photoperiods, the consumption of any autumn-winter FE altered pathways mostly related to the metabolism of cofactors and vitamins, amino acid derivates, lipids, amino acids and carbohydrates. It is important to note that the number of significantly modified routes was remarkably lower in L6 than in L18, which is consistent with the lower number of significantly altered metabolites found when administrating extracts under L6 conditions (Fig. 4).

3.3. Effect of consumption of spring-summer fruit extracts

The effects of the photoperiod in the metabolome of control animals and animals administered the spring-summer fruit extracts were studied (Supplementary Tables 27, 28). A PCA was performed to compare the two control groups and the two groups treated with the same spring-summer extract (Fig. 5a, b, c, d). PCA showed that ChE administration did not cause a notable shift in the treated groups relative to their corresponding photoperiod controls (e.g., L18-C for L18-ChE) (Fig. 5a). This was confirmed by PERMANOVA, which showed no significant differences between treated and control groups under the same photoperiod, nor any significant interaction between treatment and photoperiod (Supplementary Tables 2, 9).

PE consumption led to a clear overlap between L6-PE and L6-C, whereas L18-PE was remarkably separated from L18-C (Fig. 5b). PERMANOVA revealed a significant treatment effect and differences between L18-PE and L18-C, but not between L6-PE and L6-C (Supplementary Tables 2, 9). The interaction between photoperiod and extract consumption was statistically significant. In contrast, AE and SE administration induced a shift in the positions of both treated groups towards the same region of the plot (Fig. 5c, d). PERMANOVA results indicated a significant effect of FE consumption, and a significant interaction for AE but not for SE (Supplementary Tables 2, 9). Notably, SE administration elicited no significant metabolic alterations in L6-SE relative to L6-C. Overall, these findings suggest that AE and PE are the only spring-summer FE whose metabolic effects are photoperiod-dependent, as only these treatments exhibited a significant interaction effect. These are also the only extracts producing significant modulation under L6 conditions.

Regarding the differences at an individual-metabolite level, we constructed a set of key discriminant metabolites per fruit extract and photoperiod, using the same conditions as before (PLS-DA VIP score >1 and PERMANOVA p-value <0.05) (Fig. 5 e and Supplementary Tables 29, 30, 31, 32, 33, 34). During L18 photoperiod, AE, PE and SE sets were enriched in several amino acids. Under L6, the sets had a lower number of metabolites, suggesting a minor effect when FE are administered in L6 rather than L18, as evidenced by change ratios (Supplementary Tables 35, 36). Also, it was not feasible to identify a group of metabolites consistently altered across L6 groups.

Regarding the QEA, most of the significant changes occurred under L18 in comparison to L6 (Fig. 6a and Supplementary Tables 37, 38). At L18 photoperiod, the altered pathways were related to the metabolism of amino acids, lipids, carbohydrates, nucleotides and pathways related to oxidative stress, with L18-ChE remaining unaffected (Fig. 6b). On the other hand, treatments with ChE and SE did not trigger significant alterations in any pathway when administered at L6. Likewise, the significantly altered routes were mainly related to lipid and carbohydrate metabolism (Fig. 6c).

3.4. Association between inflammation challenge response and serum metabolome profile

To contextualize biological relevance, we used predictive modelling to associate metabolomics data with post-LPS inflammation markers (Supplementary Tables 1, 8, 9, 27, 28, 45). OPLS models yielded significant R^2 and Q^2 values for CRP and IL-10 (p-value <0.05, and both R^2 and Q^2 above 0.4) (Supplementary Table 46), indicating strong predictive performance. In the case of TNF-α and IL-6, models did not meet the significance quality thresholds. Regarding CRP and IL-10, the scores plots revealed a clear association along the first predictive component, which corresponded to differences in serum concentrations of the respective markers (Fig. 7a, b). To further investigate the most associated variables with CRP and IL-10 levels, we analysed the VIP scores of the predictive component (Supplementary Table 47). Metabolites with a VIP score greater than 1 were considered the most relevant contributors

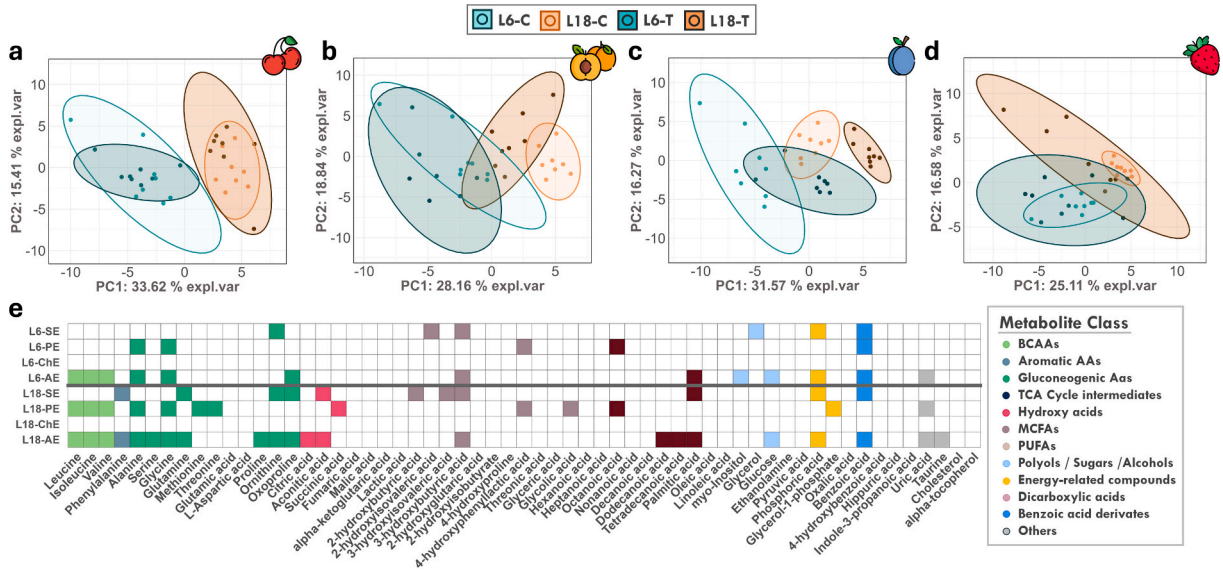


Fig. 5. Effects of spring-summer fruit extracts on serum metabolome structure and identification of key discriminant metabolites. PCA plots show the serum metabolome profiles of animals treated with ChE (a), PE (b), AE (c) and SE (d) extracts under different photoperiod conditions. (e) Tile plot displaying key discriminant metabolites for each treated group compared to their corresponding photoperiod-matched control. Only metabolites with a PLS-DA derived VIP score >1 and p-value <0.05 are coloured. Tile colour indicates the metabolite class. AAs = amino acids, AE = apricot extract, BCAAs = branched chain amino acids, C = control, ChE = cherry extract, L6 = 6 h of light, L18 = 18 h of light, MCFAs = medium-chain fatty acids, PE = plum extract, PCA = principal component analysis, PLS-DA = partial least square-discriminant analysis, PUFAs = polyunsaturated fatty acids, SE = strawberry extract, T = treated, TCA = tricarboxylic citric acid, VIP = variable importance projection.

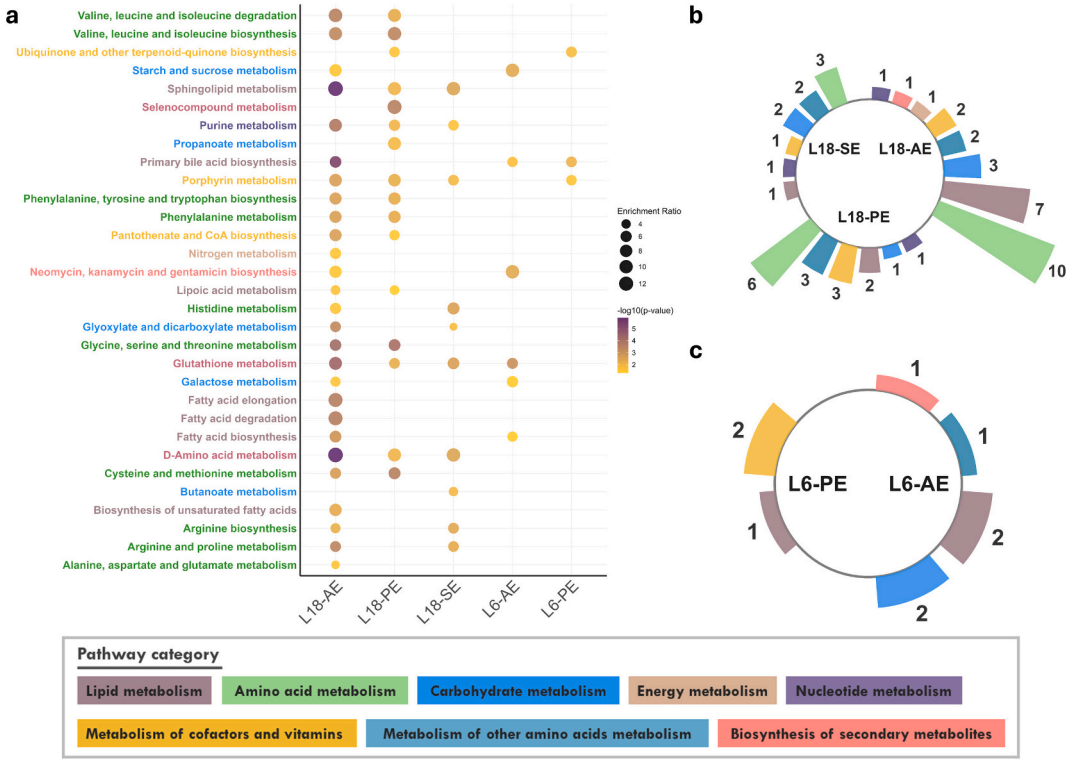


Fig. 6. Quantitative enrichment analysis of spring-summer fruit extract administration under different photoperiods. Significantly altered pathways (FDR < 0.05) are showed. KEGG was used as the reference database. (a) Bubble plot illustrates the distribution of significantly enriched metabolic pathways for L18 and L6 photoperiod conditions, following spring-summer extract administration. Each bubble represents a pathway coloured according to the BRITE hierarchy pathway category. The size of the bubble indicates the enrichment ratio, while the colour reflects the statistical significance of the alteration. Radar plots represent the number of significantly altered pathways within each pathway category for L18 (b) and L6 (c) photoperiods. The length of the bars denotes the number of altered pathways, and the colours correspond to BRITE-classified pathway categories. L6 = 6 h of light, L18 = 18 h of light, AE = apricot extract, PE = plum extract, SE = strawberry extract, FDR = false discovery rate.

to the prediction of inflammatory marker levels (Fig. 7c). Subsequently, 27 metabolites were identified as strongly associated with CRP and IL-10. This set of metabolites was predominantly enriched in amino acid species and MCFAs, and to a lesser extent in TCA cycle intermediates and hydroxy acids. Correlation analysis showed a consistent positive association between MCFAs and both CRP and IL-10, whereas most TCA intermediates and hydroxy acids were inversely correlated (Fig. 7d and Supplementary Table 48). Notably, 14 of these metabolites were also key for discriminating between L6-C and L18-C groups. Indeed, when studying the relative levels of CRP, IL-10 and discriminant metabolites, two opposing profiles were observed between L6-C and L18-C groups, suggesting a remarkable contrast in their inflammatory and metabolic states.

Regarding the FE effects, under the L18 photoperiod, autumn-winter FE consumption lowered the levels of those metabolites negatively correlated with inflammation markers and produced only moderate changes in the others, whereas spring-summer FE had little to no effect. In contrast, under the L6 photoperiod, GE, OE, and PmE shifted metabolite abundance towards the profile of the L18-C group, a pattern linked with reduced CRP and IL-10 concentrations. Conversely, KE and the spring-summer FE elicited similar effects on inflammatory markers but induced minimal changes in metabolomic profiles (Fig. 7c).

4. Discussion

Our results revealed that exposure to L6 and L18 photoperiods induced profound metabolic changes that closely resembled the expected adaptive responses to the corresponding season (i.e., L6 for winter and L18 for summer). As described in the literature, the main differences arise from the systemic orientation of metabolism (Ebling, 2014; Ebling, 2020; Helfer & Dumbell, 2020; Mariné-Casadó et al., 2018). During winter, metabolism shifts towards a more catabolic state, favouring the mobilisation and usage of energy reserves, whereas in summer, anabolic processes dominate, promoting energy storage and weight gain (Navarro-Masip, Caron, et al., 2023). These tendencies were clearly reflected in our results. Specifically, plasma levels of MCFAs and BCAAs (lipid- and protein-derived metabolites, respectively) were elevated at L6, consistent with enhanced fat mobilisation and protein degradation, as also revealed by pathway analysis. This was further evidenced by the lower final BW of animals under L6 compared with L18. Likewise, circulating BCAAs are positively associated with insulin resistance (Gasparetti et al., 2003); although F344 rats do not develop seasonal insulin resistance, as observed in other photoperiod-sensitive species, their elevation suggests reduced insulin sensitivity, thereby reinforcing the establishment of a catabolic state that is consistent with previous findings (Blanco et al., 2023; Mariné-Casadó et al., 2018; Wu et al., 2013). Notably, BCAAs mobilisation is key for the thermogenic response, a metabolic process related to cold seasons (Yoneshiro et al., 2019).

Consequently, oxidative stress is expected to increase due to the reactive intermediates generated during energy metabolism (González et al., 2023). This was supported both by pathway analysis, which revealed alterations in oxidative stress-related pathways (e.g.: glutathione metabolism), and by metabolomic markers such as MCFAs and succinate, which were elevated at L6 (Huang et al., 2021; Murphy & O'Neill, 2018; Sam et al., 2021). These metabolites have been linked to inflammation: MCFAs activate pro-inflammatory signalling, while succinate acts as an alarmin, released under mitochondrial stress to trigger anti-inflammatory responses. Together, these findings indicate a higher basal inflammatory tone during L6, in line with human

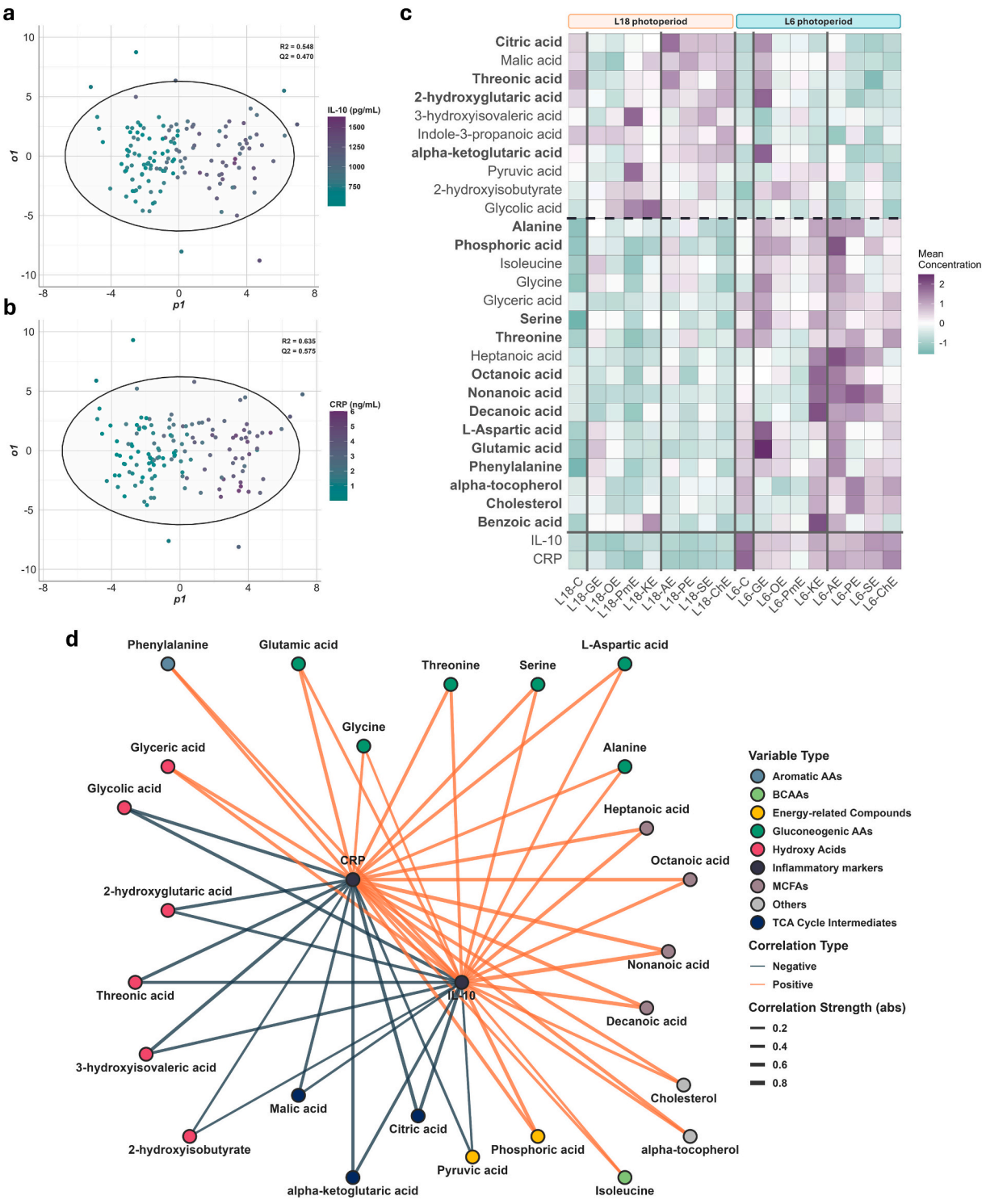


Fig. 7. Lipopolysaccharide challenge and its association with serum metabolome. Score plots of the first predictive and orthogonal components of samples based on IL-10 (a) and CRP (b) relative concentrations, as illustrated by the colour gradient. (c) Heatmap of metabolites identified as key discriminants (VIP score > 1), highlighting those which were also the most discriminant metabolites between the two control groups. The colour scale reflects the relative mean concentration across conditions. (d) Network plot representing the correlation levels between CRP and IL10, and the most important metabolites associated with them. AAs = amino acids, AE = apricot extract, BCAAs = branched chain amino acids, ChE = cherry extract, CRP = c-reactive protein, GE = grape extract, IL-10 = interleukin-10, KE = kaki extract, L6 = 6 h of light, L18 = 18 h of light, MCFAs = medium-chain fatty acids, OE = orange extract, PE = plum extract, PmE = pomegranate extract, SE = strawberry extract, TCA = tricarboxylic citric acid, VIP = variable important projection.

observational studies reporting an increased incidence of cardiovascular events in winter (Dopico et al., 2015; Ockene et al., 2004). In our model, this vulnerability was confirmed by higher levels of inflammatory markers in response to the LPS challenge under L6.

These features delineate two distinct metabotypes that responded differentially to most of the tested extracts. As with other phytochemicals, the photoperiod in which bioactive compounds are consumed critically shapes their physiological effects. This was particularly

evident for the autumn-winter extracts, with the only exception of KE. Specifically, GE, OE, and PmE shifted the metabolomic profiles of L18-treated groups towards those of the L6-C group. While at first glance this would suggest a worse metabolic output, the changes were not uniform across all metabolite groups. A consistent and common effect of these FE was the reduction of MCFA levels and other metabolites predictive of the inflammatory response. Therefore, results suggest that the administration of these FE induce a metabolic shift towards L6 conditions, with the exception that they can alleviate the higher basal inflammation characteristic of L6 and enhance the resistance to inflammatory stress, as demonstrated in the LPS challenge. In contrast, the effects of consuming spring-summer FE were comparatively mild, with no distinct metabolomic signatures or common patterns across the groups treated with the tested extracts. Although, similarly to KE, they all improved performance against the LPS challenge under L6 conditions. While the reasons underlying these differences in the intensity of action remain unclear, results are consistent with previous studies which observed differential effects of seasonal-fruit consumption depending on the photoperiod of consumption (Cruz-Carrión et al., 2022; Manocchio et al., 2024; Mariné-Casadó et al., 2019; Navarro-Masip, Manocchio, et al., 2023).

The shifts of the long photoperiod metabolomic fingerprint towards the short photoperiod pattern in those animals consuming FE from autumn-winter fruits may suggest that phytochemicals driving these effects are common to these fruits (Weng et al., 1979). Nevertheless, according to the (poly)phenolic characterization, no common compositional features were identified that could account for shared effects, suggesting that the bioactive compounds responsible for photoperiod-dependent interactions or long-term metabolic adaptations may not have been captured in our profiling. In addition, it cannot be excluded that other non-(poly)phenolic constituents present in the extracts, or higher-order interactions among multiple minor compounds, may contribute to the observed effects, although their overall contribution is likely limited given the broadly similar composition (do Valle et al., 2021). Another possible explanation is that combinations of different (poly)phenols may exert similar effects when consumed together. Despite the reasons remain unresolved, translation of our findings can have implications in several ambits. First, the actual paradigm in nutraceuticals design is based in identifying effects of phytochemicals-rich extracts or purified compounds on specific conditions or metabolic and physiological processes, thus stablishing recommendations that do not consider the seasonal response and adaptations of animal metabolism. In the view of our results, it is plausible to recommend considering the interaction between seasonality and effects of bioactive compounds in experimental designs intended to evaluate the use of (poly)phenols as nutraceuticals (do Valle et al., 2021). A practical analogy in human health comes from pharmacology, where there is a growing consensus about the need for adapting antihypertensive medications to the seasonal variations that undergo blood pressure (Stergiou et al., 2020; Stergiou et al., 2025). A second argument can be found in recommendations of healthy dietary patterns. Although in this specific field dietary recommendations often highlight the relevance of respecting natural seasonal availability of vegetal foods, considering metabolic seasonal adaptations may allow personalization of dietary recommendations according to the metabolic state of the consumer. In this sense, individual characterization at the metabolic level may inform not only on altered processes or pathways, but also about seasonal misalignments of the metabolism that can be eventually normalised by applying targeted personalised lifestyle recommendations aimed at modulating the effects of environmental factors on the person (Calderón-Pérez et al., 2024; Keijer et al., 2024).

5. Conclusions

This study highlights the profound influence of photoperiod on metabolic orientation and resilience to homeostatic disruption. These adaptations strongly condition the systemic effects of bioactive compounds, which in turn may help to mitigate seasonally associated alterations such as the heightened inflammatory tone observed under short-day photoperiod. Although the precise mechanisms underlying these regulatory effects remain to be clarified, our metabolomic data suggest that certain extracts can induce long-term metabolic adaptations, while others act primarily through more transient anti-inflammatory effects.

Taken together, these findings reinforce the concept that bioactive compounds constitute a fundamental component of the diet and open the door to seasonally aware nutritional recommendations. Nevertheless, further research is required to establish the robustness of these effects and to identify the key compounds behind this pattern. In addition, the potential role of other exposome constituents in modulating dietary responses needs consideration. Finally, the influence of fruit harvest season remains an open question, with our results suggesting that autumn-winter-harvested fruits may contain more potent bioactives, a hypothesis that may deserve deeper investigation.

5.1. Limitations of the study

While this study elucidates how seasonally-conditioned metabolic states influence the response to dietary (poly)phenols, several aspects merit further investigation. Given the exploratory nature of this work and the high number of dietary treatments, a male-only model was selected to minimize the total animal count. While this strategy aligned with ethical reduction principles, it precludes insights into sex-specific differences, underscoring the need for future studies in females. Furthermore, while photoperiod manipulation effectively drives metabolic rhythmicity, it represents only one seasonal component. Future research should consider exposome factors like ambient temperature for a more holistic seasonal simulation. Finally, deeper characterization of these complex fruit extracts is needed to elucidate the specific (poly)phenols driving the observed metabolic and anti-inflammatory shifts.

CRediT authorship contribution statement

Alberto Domingo-Gómez: Writing – original draft, Methodology, Investigation, Formal analysis. **Francesca Manocchio:** Writing – review & editing, Methodology, Investigation. **Diego Morales:** Writing – review & editing, Methodology, Investigation. **Anna Arola-Arnal:** Writing – review & editing, Funding acquisition, Conceptualization. **Francisca Isabel Bravo:** Writing – review & editing, Supervision, Conceptualization. **Begoña Muguerza:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Josep M. del Bas:** Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodres.2026.119854.

Data availability

Data will be made available on request.

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