Molecular Nutrition & Food Research

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RESEARCH ARTICLE OPEN ACCESS

Photoperiod-Dependent Effects of Phenolic-Enriched Fruit Extracts on Postprandial Triacylglyceride Levels and Acute Inflammatory Responses in F344 Rats

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Received: 31 December 2024 | **Revised:** 10 April 2025 | **Accepted:** 8 May 2025

Funding: This work was supported by Grant number PID2020-113739RB-I00 funded by MCIN/AEI/10.13039/501100011033.

Keywords: anti-inflammatory activity | dyslipidaemia | LPS | OLTT | (poly)phenols | seasonality

ABSTRACT

This study investigated the photoperiod-dependent effects of eight phenolic-enriched fruit extracts on postprandial blood triacylglyceride (TAG) levels and serum cytokine and CRP levels in F344 rats after an oral lipid tolerance test (OLTT) and lipopolysaccharide (LPS)–induced inflammatory challenge, respectively. Animals were exposed to short (6-h light, L6) or long (18-h light, L18) photoperiods and orally supplemented with fruit extracts (100 mg/kg) for 2 weeks. Extracts were obtained from seasonal fruits (cherries, plums, apricots, strawberries, persimmon kakis, grapes, oranges, and pomegranates). Temporal homeostasis disruption was induced by an OLTT and LPS challenge. No differences in blood postprandial TAG levels were observed in the L6- and L12-control groups. However, in the experimental groups, the postprandial TAG response depended on the photoperiod and fruit extract consumption, mainly cherry and plum extracts in L6 ($p < 0.05$). In addition, control rats exposed to L6 exhibited higher blood IL-6 and TNF-α levels after inducing LPS-inflammatory response. Notably, winter-fruit and strawberry extracts were the most efficient at lowering proinflammatory cytokines. These findings show the effectiveness of specific fruit extracts in modulating postprandial TAG levels and acute inflammatory responses, being their effects photoperiod-dependent, opening the door to the design of functional ingredients specific for each season.

1 | Introduction

Noncommunicable diseases are a significant public health problem that cause 74 million deaths annually, corresponding to 74% of global deaths [1]. Their incidence is increased by various metabolic factors, such as obesity, raised blood pressure, and high blood glucose and lipid levels, as well as behavioral factors, including sedentary lifestyle, alcohol and tobacco consumption, and unhealthy diet [2, 3]. Features related to obesity, such as high waist circumference, dyslipidemia, insulin resistance, and

Abbreviations: AUC, areas under the curve; CRP, C-reactive protein; F344 rats, Fisher 344 rats; GSPE, grape seed proanthocyanidin-rich extract; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; OLTT, oral lipid tolerance test; TAG, triacylglyceride; TNF-α, tumor necrosis factor-alpha.

hypertension, are some of the criteria used to diagnose metabolic syndrome (MetS). Moreover, circulating inflammatory cytokines are associated with the expansion of adipose tissue in obese individuals and are considered useful biomarkers for predicting noncommunicable diseases [4].

Changes in lifestyle and dietary patterns through the acquisition of healthier choices may prevent weight gain and alleviate noncommunicable disease comorbidities [5]. Low consumption of plant-based foods has been associated with a higher risk of developing diseases, including obesity, diabetes, and cardiovascular diseases [6]. In contrast, the consumption of vegetables and fruits was inversely associated with diastolic blood pressure and MetS risk [7–9]. These plant-based foods contain diverse bioactive compounds, such as phenolic compounds. Their consumption has been associated with anti-inflammatory effects, improvements in glucose and blood pressure control, reduction in low-density lipoprotein cholesterol (LDL-C) oxidation and triacylglyceride (TAG) levels, body mass index, and waist circumference [10–12]. However, their effects on health may vary depending on the type of (poly)phenol consumed, the dose, or the (poly)phenol profile when consumed in an extract or plant-derived product. Furthermore, this phenolic profile can vary depending on several factors such as species or environmental factors, among others [13]. Interestingly, recent studies have shown that the beneficial effects of phenolic compounds, administered as phenolic extracts or phenolic-rich fruits, can vary depending on the photoperiod during which they are consumed [14, 15]. Xenohormesis theory proposes that certain plant-based compounds, such as phenolic compounds, may act as signaling molecules, providing information about external environmental conditions to consumers. These signals would help modulate metabolic, physiological, and behavioral processes, aiding the adaptation of consumers to environmental changes [16–18]. In this regard, in a previous study, our group obtained eight phenolic-enriched fruit extracts from seasonal fruits, which modulated blood biochemical markers, including TAG, cholesterol, and fasting glucose levels in Fisher 344 (F344) rats after 2 weeks of consumption [19]. Interestingly, their properties depended not only on the phenolic composition of the extract but also on the photoperiod of consumption [19]. Specifically, cherry and apricot extracts lowered blood TAG levels exclusively when consumed under a short photoperiod. Meanwhile, pomegranate, grape, and orange extracts reduced cholesterol and fasting glucose levels in animals exposed to a short photoperiod [19]. However, it is unknown if these extracts can exert beneficial effects on postprandial TAG levels and inflammatory response in animals subjected to different metabolic stress conditions. Elevated postprandial TAG and inflammation, if prolonged, can increase the risk of cardiovascular disease [20, 21]. It could be useful to evaluate the potential of these extracts as functional ingredients for the prevention of MetS-associated diseases.

Moreover, their effects may be different considering the results of our previous study and that blood biochemical markers, such as TAG or glucose, can be affected by the photoperiod in F344 rats. In addition, another study showed that humans can have different inflammatory statuses depending on the season, and fruit consumption can reduce the levels of C-reactive protein (CRP) depending on the season of consumption [22].

Different metabolic challenge tests have been designed to evaluate the effects of bioactive compounds on the main metabolic alterations. In response to metabolic stressors, an organism aims to restore balance and elicit a strong and rapid response [23]. Consequently, the measurement of the stress response reaction will be helpful in determining the efficacy of bioactive compound administration. It is considered a sensitive method for assessing changes in health status in response to interventions. A commonly utilized challenge test is the oral lipid tolerance test (OLTT), which allows monitoring of lipid metabolism [24]. In addition, lipopolysaccharide (LPS)–induced inflammatory challenges have been extensively used to study the anti-inflammatory potential of drugs and natural compounds [25]. LPS activates macrophages/monocytes and induces the release and production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6, as well as CRP [26]. These proinflammatory cytokines are protein molecules normally secreted by different cell types (mainly macrophages) as part of inflammatory responses, while CRP is an acute-phase protein with markedly elevated levels under inflammatory conditions, often clinically measured to evaluate inflammation severity [27, 28].

Therefore, the objective of the present study was to evaluate the effects of eight fruit extracts on postprandial lipid metabolism and inflammatory responses in F344 rats subjected to different metabolic challenge tests to temporarily induce disturbances in homeostasis. In addition, animals will also be exposed to a short (6-h light, L6) and long (18-h light, L18) photoperiods to evaluate potential changes in the effectiveness of these extracts depending on the photoperiod of consumption.

2 | Materials and Methods

2.1 | Seasonal-Fruit Extracts

Fruit extracts were obtained as described in Manocchio et al. [19]. Ripe summer (cherry (*Prunus avium* L.), apricot (*Prunus armeniaca*), strawberry (*Fragaria vesca* L.), plum (*Prunus domestica*) and winter fruits (grape (*Vitis vinifera*), orange (*Citrus sinensis* L.), persimmon (*Diospyros kaki*), and pomegranate (*Punica granatum*) were acquired during the summer and winter seasons, respectively, from local producers. Pedicels were manually removed, and whole fruits, including the skin, seed, and pulp, were mechanically triturated and mixed to obtain homogenates of strawberry and grapes. For cherry, apricot, plum, and persimmon, seeds were removed before trituration, and for orange and pomegranate, the skin was removed before being triturated. The homogenates were stored at −20°C until the extraction process.

The proximate composition (protein, ash, fiber, and fat contents) of original fruits and extracts is listed in Manocchio et al. [19]. Phenolic composition of the fruit extracts determined using HPLC-Diode Array Detection-Electrospray Ionization-Tandem mass spectrometry is also listed in Manocchio et al. [19]. Briefly, the main phenolic family found in grape and cherry extracts were anthocyanins, with cyanidin-3-rutinoside and malvidin-3-*O*-monoglucoside, respectively, being the most abundant phenolic compounds. Strawberry and pomegranate extracts contain mainly phenolic acids, being the major compounds being ellagic

acid rhamnoside and ellagic acid in the strawberry extract, and punicalagin and pedunculagin in the pomegranate extract. In the case of the apricot and orange extracts, the most abundant families were flavonols and flavanones, respectively, with rutinoside and didymin as the major components, respectively, whereas the plum extract stood out by its flavanol content, mainly by its content in procyanidin dimers. Phenolic compounds were not identified in the persimmon kaki extract owing to its low concentration [19].

2.2 | Experimental Designs

After 1 week of adaptation, 8-week-old F344/IcoCrl rats (Charles River Laboratories, L'Arblese, Cedex, France) were exposed to a L6 and L18 ($n = 72$ per group) to simulate winter and summer seasons, respectively. This substrain of F344 rats has shown to be responsive to photoperiods [14, 29, 30]. During the experiment, all animals were provided with a regular chow diet (AO4; Panlab, Barcelona, Spain) and had access to tap water on demand.

Experiment 1: After 4 weeks of photoperiod adaptation, rats were supplemented daily with the fruit extracts or tap water (control, C group) for 2 weeks ($n = 8$ per group). After 12 h of fasting, the animals were subjected to the OLTT. For that, they were administered either the extracts (100-mg/kg BW) or tap water, and 3 h later, they were orally given lard oil by gavage (2.5-mL/kg BW). TAG levels in blood from the tail vein were analyzed using an Accutrend Plus instrument (Roche Diagnostics, Barcelona, Spain) at 0, 30, 60, 120, and 240 min.

Following the principle of 3 R's, only micro-sampling of blood was performed, and the animals were used again in the following experiment after 4 days of washing out, where they were not supplemented with extracts.

Experiment 2: Rats were daily administered fruit extracts or tap water (C) daily for 2 weeks ($n = 8$ per group). The final day of the experiment involved administering LPS at a dose of 0.5-mg/kg BW to the animals 3 h after the treatment. Four hours later, the rats were killed by decapitation. Serum was obtained by centrifuging nonheparinized blood at $3000 \times g$ for 15 min at room temperature and stored at −80°C until it was needed for the study. Serum inflammatory markers such as TNF-α, IL-6, CRP, and anti-inflammatory marker IL-10 levels were determined using Finetest ELISA kits following the manufacturer's instructions (Labclinics, Barcelona, Spain). All analyses were performed in duplicates. A diagram of the experimental design is displayed in Figure 1.

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 | Extract Administration and Dosage Information

Fruit extract consumption by the animals was voluntary, linking them to a syringe. Fruit extracts were administered between 8:00 a.m. and 9:00 a.m., consistently at the same time each day and coinciding with the animals' light cycle, which began at 7:00 a.m. (lights on). The control group was administered an equal volume of tap water, following the same procedure.

The animals received the corresponding fruit extracts at a dose of 100-mg/kg body weight (BW). This dose was chosen based on a previous study, which showed that this amount of extract was able to modulate different blood biomarkers in healthy F344 rats [19]. Considering the translation of animal to human doses and estimating the daily intake for a 70-kg human [31], an extract dose of 100 mg/kg/day corresponds to an intake of approximately 1120 mg of phenolic-enriched extract per day [31]. The daily intake of phenolic compounds in human diets can vary widely depending on dietary habits, and it is estimated to be between 200 and 1000 mg per day [32], being the studied dose above this average estimation.

2.4 | Statistical Analysis

Values are expressed as the mean ± standard deviation (SD). Outliers were identified and removed before statistical analysis. Two- and one-way analyses of variance (ANOVA) were used to determine differences among groups using the Post Hoc Tukey test. Two-way ANOVA is indicated as P: photoperiod effect, E: extract effect, P × E: interaction between photoperiod and extract when $p \leq 0.05$. Student's t-test was used to identify significant differences ($p < 0.05$) produced by the photoperiod for each treatment. All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) software (SPSS Inc., Chicago, IL, USA).

3 | Results and Discussion

Several strategies have been proposed for the prevention of MetS, including a nutritional approach to the consumption of diets rich in bioactive compounds such as fruits and vegetables [7]. Fruits are rich in phenolic compounds, which play an important role in preventing metabolic disorders [33]. In this regard, consuming whole fruits and some phenolic-enriched extracts, such as a grape seed proanthocyanidin-rich extract (GSPE), can improve obesity-related outcomes. For instance, GSPE supplementation reduced adipocyte size and increased adipocyte number in an obese rat model [34]. However, studies on F344 rats have shown that these effects can vary depending on the photoperiod of consumption [17].

Accordingly, the modulation of different blood markers in healthy rats by eight novel seasonal fruit extracts was recently shown to depend not only on the phenolic composition of the extract, but also on the photoperiod of consumption [19]. However, the effects of these fruit extracts on metabolic alterations remain unclear. Therefore, the present study focused on investigating the effects of eight seasonal-fruit extracts administered to F344 rats exposed to different photoperiods for 2 weeks, when metabolic alterations were performed through OLTT and LPS-induced inflammatory challenges.

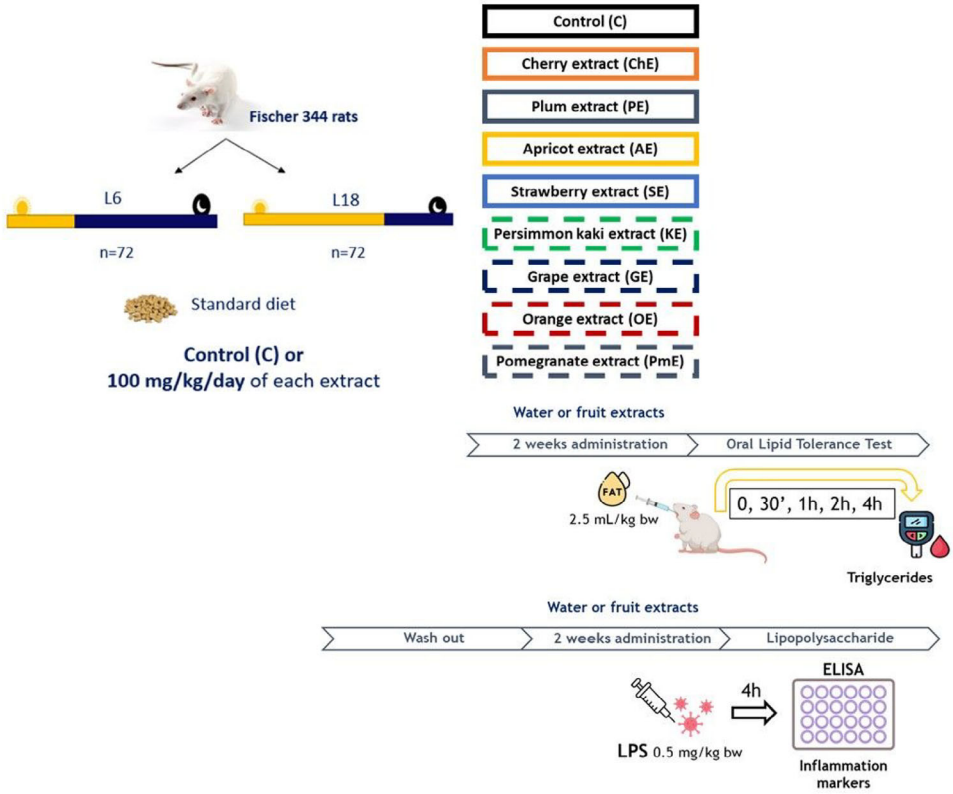

FIGURE 1 | Experimental design carried out in Fischer 344 (F344) rats exposed to different photoperiods and subjected to different metabolic challenges.

3.1 | Fruit Extracts Improved Postprandial Lipid Response Depending on the Photoperiod

OLTT is an efficient method for evaluating lipid metabolism in the body after lipid-induced hypertriglyceridemia [35]. The ability to reduce TAG levels after lipid ingestion provides information on intestinal lipid absorption, transport, and metabolism [36]. An increase in postprandial TAG levels is associated with the development of cardiovascular disease [37]. Thus, this challenge test is an efficient method for evaluating the anti-hypertriglyceridemic potential of bioactive compounds. In the present study, the statistical analysis of the areas under the curve (AUC) obtained from representing blood TAG levels of animals subjected to OLTT showed a significant photoperiod effect and a tendency in the interaction between fruit extracts and photoperiod (two-way ANOVA, $p \leq 0.05$, and $p = 0.06$, respectively, Figure 2A,B). No significant differences were observed in AUC between the two control groups (Figure 2A,B). However, in our previous studies, we observed that healthy F344 rats showed increased levels of blood TAG in the L6 photoperiod (213 mg/dL) compared to the L18 photoperiod (155 mg/dL) [38]. These photoperiodic differences seem to dilute after the OLTT challenge. Seasonal fluctuations in circulating LDL-C, glucose, and blood pressure levels have been observed in patients with diabetes, with higher levels occurring in winter compared to summer [39]. Additionally, seasonal- and sex-dependent changes in total circulating lipid levels, but not in TAG or cholesterol levels, were observed in female *Tropidurus catalanensis* [40]. Moreover, specific genes related to glucose and lipid metabolism changed their expression due to differences in photoperiods and seasonality, such as Sirtuin 1 (*Sirt1*), with higher gene expression in L6 photoperiod [41].

Regarding the effects of extracts on blood TAG levels after OLTT, the extracts obtained from two summer fruits, cherry and plum, significantly lowered the serum TAG levels in rats exposed to L6 (65.6 and 74.4 mg/dL × s, respectively) compared to the L6-C group (106.6 mg/dL × s) (Figure 2A). However, none of the fruit extracts changed the postprandial lipid response in the L18-exposed animals after OLTT compared to that in the L18-C group (Figure 2B). In line with these results, a previous study using the same cherry extract found a reduction in blood TAG levels in healthy F344 rats only when administered during the L6 photoperiod showing a 27% decrease from 223 to 163 mg/dL [19]. Interestingly, the beneficial effect of whole cherries, such as tart and sour cherries, on postprandial TAG levels had already been reported in a clinical study, although without considering the time of the year of consumption [42]. However, the administration of sweet cherry (100 mg/kg BW daily for 7 weeks) to F344 rats did not affect blood TAG levels [43]. This lack of whole cherry effects on TAG levels could be due to differences in the (poly)phenols administered to the animals [19]. Thus, although F344 rats in both studies consumed the same amount of the product, the extract dose contained more phenolic compounds than the fruit dose. Moreover, the cherry extract was enriched in anthocyanins [19], which could be involved in the effect of the cherry extract on TAG levels, since previous studies have shown that anthocyanin intake improved dyslipidemia in healthy populations [44]. Moreover, cyanidin-3-rutinoside emerged as the main phenolic compound

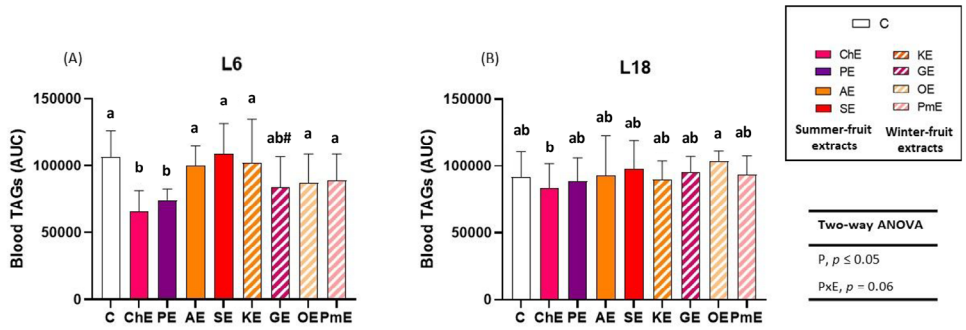

FIGURE 2 | Oral lipid tolerance test (OLTT). Blood triacylglyceride (TAG) levels, represented as the area under the curve (AUC), of 12h-fasted Fischer 344 (F344) rats exposed to short (L6, 6-h light, A) or long (L8, 18-h light, B) photoperiods and administered water (control, C) or 100-mg/kg body weight (BW) of cherry (Ch), plum (P), apricot (A), strawberry (S), persimmon kaki (K), grape (G), orange (O), and pomegranate (Pm) extracts (E) for 2 weeks ($n = 8$ per group, mean ± standard deviation). OLTT was performed after 3-h post-treatment administration through the oral administration of lard oil (2.5-mL/kg BW) to animals, and tail blood was analyzed at different times (0–240 min). Different letters indicate significant differences between groups for a specific photoperiod (one-way ANOVA, Post Hoc Tukey's test, $p \leq 0.05$). Two-way ANOVA analysis was used to examine differences between all groups: P (photoperiod effect); E (fruit-extract effect); P × E (interaction between photoperiod and extract) (Post Hoc Tukey's test, $p \leq 0.05$). # indicates tendency differences between the same control or extract administered in the L6 or L18 photoperiods (Student's *t*-test, $p > 0.05$–< 0.01).

present in the cherry extract [19]. This compound inhibited in vitro pancreatic lipase and cholesterol esterase activity and reduced cholesterol intake in Caco-2 cells treated with this compound [45].

Regarding the effects of the plum extract, plums are known for their high content of proanthocyanidins and chlorogenic acids [46]. Similarly, proanthocyanidin dimers were the major compounds in the plum extract obtained in the present study [19]. Previous studies have shown that grape seed extracts rich in proanthocyanidins attenuated the development of cardiometabolic risk factors (high blood pressure, BW, waist perimeter, lipid metabolism markers) in Wistar rats [47]. In addition, several clinical studies showed that plum supplementation significantly reduces LDL-C levels; however, no effects were observed on lowering TAG levels among healthy and overweight patients supplemented with different dosages [48]. These results are in contrast with those of our study, in which plum extract reduced TAG levels. The plum extract was enriched in phenolic compounds compared to the whole plum [19] therefore, in addition to the in vivo model and duration of treatment, an increase in the content of phenolic compounds administered to animals (plum extract vs. whole fruit) could explain the different effects observed between the whole fruit and the extract.

Little is currently known about the potential mechanisms of action involved in the photoperiod-dependent effects of the (poly)phenol-rich extracts on TAG levels. However, it has been observed in a knockout mouse model (Farnesoid X receptor $(FXR)^{-/-}$ mice) that the reduction in TAG levels observed due to ingestion of an extract rich in grape seed (poly)phenols was FXR-dependent [49]. FXR plays a crucial role in hepatic lipid homeostasis, and its transcription exhibits circadian rhythm [50]. Moreover, this nuclear receptor is regulated by sirtuins [51], whose activity is modulated by phenolic compounds [52] and follows daily oscillations [53]. Circadian rhythms are endogenous oscillations that occur autonomously, although they are reset by various external cues—among which daylight, which defines photoperiods, is the most prominent [54]. Another potential explanation for the varying effects of phenolic compounds depending on the photoperiod of consumption could be their interaction with gut microbiota. Moreover, Bacteria species, such as *Escherichia coli*, *Bifidobacterium* sp., *Lactobacillus* sp., *Bacteroides* sp., and *Eubacterium* sp. can metabolize phenolic compounds, producing different phenolic-derived metabolites [55]. These phenolic metabolites can be absorbed and confer health benefits [55]. Moreover, these compounds can regulate ileum FXR levels [56]. Notably, recent studies have reported differences in the gut microbiota composition of F344 rats exposed to different photoperiods, which may lead to the production of distinct metabolites [57]. Furthermore, a recent study showed that the gut microbiota mediates the photoperiod-dependent effects of proanthocyanidin bioavailability in obese F344 rats [58]. This may also contribute to the differential effects of the studied fruit extracts. Nevertheless, further research is required to elucidate the mechanisms underlying the effects of phenolic-rich fruit extracts.

It is worth mentioning that the cherry and plum extracts reduced TAG levels only when administered during the L6 photoperiod. Therefore, these findings suggest that the season of consumption should be taken into consideration to optimize the efficacy of these phenolic-enriched fruit extracts. Moreover, the fact that the effects were observed in the short photoperiod is also considered relevant because metabolic-related outcomes are more frequent during winter months in humans [59]. Therefore, the present results suggest that cherry and plum extracts might be good candidates for their use as supplements or functional food ingredients to lower blood postprandial TAG levels during the winter season.

3.2 | Photoperiodic Modulation of Circulating Inflammatory Cytokines by Fruit Extracts

Intestinal inflammation is a relevant outcome for obesity and metabolic disorders, primarily due to a defective barrier function that promotes endotoxin entry, causing a chronic and systemic

inflammatory state [60]. Indeed, gut permeability is strictly influenced by microbiota composition, which in turn is affected by diet [61]. For instance, high-fat diet intake has been strongly correlated with adipose tissue expansion and an increase in several inflammatory cytokines, such as IL-6, IL-1, TNF-α, and acute-phase proteins, such as CRP [62].

In the present study, an LPS-induced inflammatory challenge was performed to simulate systemic inflammation. The objective of this study was to study the potential anti-inflammatory effects of seasonal-fruit extracts in a photoperiod-dependent manner. Previous studies have mentioned that inflammation can occur during the winter in humans. Dopico et al. [63] found seasonal gene expression patterns in immune cells and adipose tissues across diverse populations, noting an inverse expression profile between European and Oceanian groups. Notably, Europeans showed increased gene expression levels of IL-6 and CRP during winter [63]. Moreover, there is a proinflammatory status during a short photoperiod in the *pars tuberalis* of the ewe in photoperiod-responsive species, also related to a significantly higher expression of proinflammatory genes such as *IL6*, *TNF*, *IL6ST*, *TNFRSF1A*, and *TNFRSF1B* [64].

TNF-α, a proinflammatory cytokine that stimulates macrophage response in the presence of LPS [65], was one of the key biomarkers evaluated. A significant interaction between photoperiod and an extract consumption effect was observed (two-way ANOVA, P, E, P × E, $p \leq 0.05$). Serum TNF-α levels were more than two times higher in rats under winter light/dark schedule (L6-C group) than those under L18 (L18-C group), 2,197.3 and 853.4 pg/mL, respectively (Figure 3A,B). This fact suggests that the inflammatory state is favored under the winter light/dark schedule. Seasonal variations in circulating TNF-α levels were also found in northern palm squirrels; however, the levels were higher in summer than in winter [66]. Regarding the effects of the extracts on this inflammatory marker, serum TNF-α levels ranged between 427.5 and 2197.3 pg/mL in the supplemented L6-exposed animals, and between 714.0 and 1453.2 pg/mL in the supplemented L18-exposed rats (Figure 3A,B, respectively). Winter fruit extracts (persimmon kaki, grape, orange, and pomegranate) and one summer fruit extract (strawberry) significantly decreased TNF-α levels when administered to L6-exposed rats in comparison with the L6-C group (Figure 3A). However, most extracts did not affect TNF-α levels in L18-exposed animals, except for persimmon kaki, apricot, and strawberry extracts, which increased TNF-α levels with respect to the L18-C group, tending to counteract the photoperiod effect (Figure 3A,B). Notably, a differential photoperiod-dependent effect was observed after the consumption of the strawberry extract ($p \leq 0.05$, Student's *t*-test), as TNF-α levels were reduced in the L6 photoperiod, whereas it exerted an opposite effect in the L18 photoperiod (Figure 3A,B). Previous studies conducted in preclinical models have observed that supplementation with a combination of fruits and vegetables reduced serum TNF-α concentrations in a 12:12 light/dark schedule [67]. Fruit intake, like strawberries, is associated with improved antioxidant markers and endothelial function; by decreasing inflammation markers in humans [68]. Among the eight fruit extracts, strawberry, grape, and pomegranate extracts showed the strongest in vitro antioxidant activity (pomegranate > grape > strawberry) [19], potentially contributing to their anti-inflammatory effect during L6. Furthermore, several studies performed on fruits have observed a photoperiod-dependent effect on several metabolic biomarkers involved in glucose and lipid metabolism [38, 69, 70]. However, this is the first time that the anti-inflammatory effects of extracts containing phenolic compounds have been shown to depend on the photoperiod during which they are consumed.

As a nonspecific response to obesity, the liver produces CRP, whose levels are modulated by different dietary patterns [71]. A high intake of cholesterol is associated with increased CRP levels [72], whereas a Mediterranean diet, rich in bioactive compounds, is associated with decreased CRP levels [73]. Furthermore, an inverse correlation between the consumption of several fruits and blood CRP levels has been observed in patients suffering MetS [74]. In the present study, a photoperiod and extract consumption effects and interaction between both factors were observed (two-way ANOVA, P, E, P × E, $p \leq 0.05$). Specifically, serum CRP levels were higher in the L6-C group than in the L18-C group (Student's *t*-test, $p \leq 0.05$) (Figure 3C,D). High CRP levels in humans have been associated with the winter season, suggesting that light hours could play a role in the inflammatory state [75]. In addition, all fruit extracts, except cherry, decreased serum CRP levels when consumed during the L6 photoperiod, with the pomegranate extract being the most effective in lowering this inflammation marker (0.24 ng/mL) (Figure 3C). However, the consumption of a pomegranate juice did not show any improvement in CRP blood levels of volunteers [76]. Differences between studies might be due to differences in the experimental model, time of consumption, or the different phenolic profile of the whole fruit and the extract, taking into account that pomegranate extract was enriched with phenolic compounds [19]. An inverse correlation between the consumption of food with in vitro antioxidant activity and serum CRP levels was observed in young Japanese women [77]. Our previous study showed that this extract had the highest in vitro antioxidant capacity among the tested fruit extracts [19]. Other studies have also demonstrated the anti-inflammatory activity of different (poly)phenol-rich extracts in several cell and animal models [78]. Moreover, a negative correlation was also found between antioxidant activity and nitric oxide production of LPS-induced RAW 264.7 cells treated with a black raspberry seed extract, containing ellagitanins [79]. Ellagitanin derivatives were the main phenolic compounds in the pomegranate extract. Therefore, the antioxidant capacity of this extract might be involved in its anti-inflammatory effects.

Regarding the L18 photoperiod, all extracts produced changes in serum CRP levels compared to the control group, except for cherry and grape extracts. In this regard, plum, apricot, strawberry, pomegranate, and orange extracts decreased CRP levels compared to the L18-C group, whereas persimmon kaki extract increased it (Figure 3D). Thus, pomegranate extract significantly lowered CRP levels in both photoperiods. Among the fruits used in this study, strawberries are one of the fruits with the highest content of (poly)phenols and antioxidant capacity [80]. Their consumption has been associated with several beneficial effects, such as antimicrobial, antioxidant, and antihypertensive effects [81], and is inversely correlated with CRP levels in humans [82], which agrees with the results of this study. Overall, most fruit extracts reduced CRP levels, although this effect depended on the fruit extract and photoperiod of consumption. Differences between extracts could be attributed to the different phenolic profiles shown by the eight extracts [19], since the phenolic profile

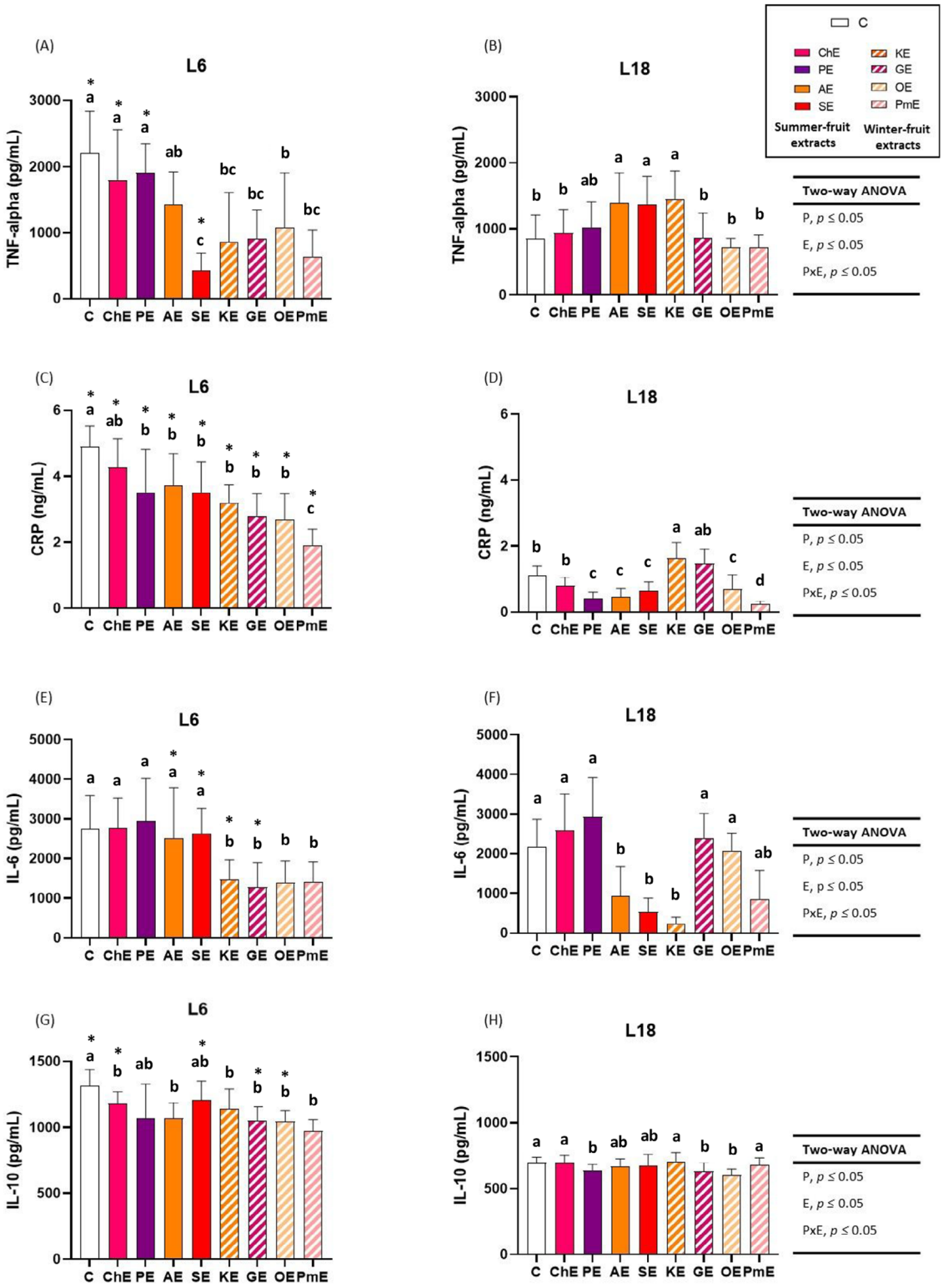

FIGURE 3 | Lipopolysaccharide (LPS) challenge. Serum tumor necrosis factor alpha (TNF-α, A and B), C-reactive protein (CRP, C and D), interleukin-6 (IL-6, E and F), and IL-10 (G and H) levels of Fischer 344 (F344) rats exposed to short (L6, 6-h light, A, C, E, and G) or long (L8, 18-h light, B, D, F, and H) photoperiods and administered water (control, C) or 100-mg/kg body weight (BW) of cherry (Ch), plum (P), apricot (A), strawberry (S), persimmon kaki (K), grape (G), orange (O), and pomegranate (Pm) extracts (E) for 2 weeks ($n = 8$ per group, mean ± standard deviation). LPS-induced inflammatory response was performed after 3-h post-treatment administration through the intraperitoneal injection of LPS (0.5-mg/kg BW) to animals. Different letters indicate significant differences between groups for a specific photoperiod (one-way ANOVA, Post Hoc Tukey's test, $p \leq 0.05$). Two-way ANOVA analysis was used to examine differences between all groups: P (photoperiod effect); E (fruit-extract effect); P × E (interaction between photoperiod and extract) (Post Hoc Tukey's test, $p \leq 0.05$). * indicates differences between the same control or extract administered in the L6 or L18 photoperiods (Student's *t*-test, $p \leq 0.05$).

of a fruit, vegetable, or extract has been shown to be key to its ability to exert biological properties [83].

Moreover, levels of IL-6 were determined in the present study. This circulating inflammatory cytokine, which is associated with obesity and the incidence of cardiovascular diseases [84], can be reduced with the consumption of foods rich in phenolic compounds [85]. In the present study, IL-6 levels were affected by both photoperiod and extract consumption, and an interaction between both factors was also detected (two-way ANOVA, P, E, P × E, $p \leq 0.05$) (Figure 3E,F). Seasonal variations in human blood IL-6 levels were observed, being more elevated in winter and summer than in other seasons [86]. In contrast, the opposite pattern was found in northern palm squirrels, where circulating IL-6 levels were higher in summer than in winter [66]. All winter-fruit extracts (persimmon kaki, orange, grape, and pomegranate extracts) decreased serum IL-6 levels in L6-exposed rats with respect to the L6-C group, suggesting a relationship between the consumption of winter-fruit extracts and their anti-inflammatory properties only under the winter light/dark schedule. Moreover, apricot, strawberry, and persimmon kaki extract reduced IL-6 levels under the L18 (Figure 3F). In agreement with our results, other studies have reported effects of the consumption of several fruits or fruit-derived (poly)phenols on interleukins in several experimental models [87, 88]. For instance, in a model of MetS in zebrafish, persimmon kaki downregulated *Il6* gene expression [89]. In addition, a clinical study showed that after the ingestion of high-fat foods, proinflammatory cytokines levels were increased in blood, and orange fruit supplementation partially counteracted inflammation by lowering proinflammatory cytokine secretion, such as IL-17, but not IL-6 [90]. Controversial effects on IL-6 after consumption of pomegranate-derived products have been reported. In this regard, IL-6 levels were reduced after treated inflamed Caco-2 cells with an extract obtained from pomegranate shell (containing punicalagin, an ellagitanin derivative compound) or pure punicalagin [87]. The most relevant phenolic compounds in the pomegranate extract were ellagitanin acid derivatives, mainly pedunculagin and punicalagin [19]. In humans, reduced blood IL-6 were observed in hemodialysis patients (55–81 years old) and type-2 diabetic patients after the intake of pomegranate juices (100 mL/day/12 months and 50 g/day/4 weeks, respectively); however, no effects in this cytokine were observed in hypertensive patients after the consumption of a pomegranate juice (100 mL/day/1 day) or in hemodialysis patients (47–75 years old) after the intake of a pomegranate juice (100 mL/day/ 4 weeks) or pomegranate extract (POMx, 1050 mg/day/4 weeks) [91].

In addition, our study revealed photoperiod-dependent effects on IL-6 levels in most fruit extracts. In this regard, the anti-inflammatory effects of the apricot, strawberry, and grape extracts depended on the photoperiod of consumption; however, the anti-inflammatory effects of the persimmon kaki extract were independent of the photoperiod of consumption (Figure 3E,F). These results highlight the link between seasonal rhythms and fruit extracts enriched in (poly)phenols.

Finally, IL-10 levels, an anti-inflammatory cytokine [92], were also evaluated in the present study. IL-10 levels were almost two times higher in most of the L6 groups studied than in the L18 groups (except for plum and apricot extracts; $p \leq 0.05$, Student's *t*-test). Moreover, neither of the fruit extracts increased IL-10 levels in any photoperiod. Nevertheless, all winter-fruit extracts, together with cherry and apricot extracts, reduced serum IL-10 levels in the L6 photoperiod, whereas orange, plum, and grape extracts reduced them in the L18-photoperiod (Figure 3G,H). These results could be attributed to the number of hours after LPS injection; indeed, after 4 h of induced inflammation, the anti-inflammatory cytokine response did not reach its peak concentration [93].

There is limited information on the mechanisms involved in the photoperiod-dependent effect of polyphenols on inflammation. Several studies have observed that phenolic-rich extracts can exert anti-inflammatory effects by modulating the NF-κB and Nrf2 pathways [94]. NF-κB, a nuclear transcription factor, is a key regulator of the inflammatory process [95], while Nrf2 controls the expression of various genes involved in antioxidant defense, detoxification, and anti-inflammatory processes [96]. Additionally, phenolic compounds have been shown to regulate various protein kinases, including extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK), and AMP-activated protein kinase (AMPK), which influence the activity of transcription factors such as Nrf2 and NF-κB [97]. Melatonin, which plays a crucial role in the regulation of seasonal rhythms, also exhibits anti-inflammatory effects by modulating some of these signaling pathways, including JNK, NF-κB, and Nrf2 [98, 99]. Moreover, similar to the effect on TAG levels, other mechanisms that should be considered are the interplay between gut microbiota, phenolic compounds, and photoperiod. In addition, gut microbiota can also generate metabolites with anti-inflammatory properties [100]. However, further research is needed to understand the mechanisms involved in the effects of phenolic-rich fruit extracts.

4 | Conclusions

Fruit extracts may be interesting candidates for preventing or treating metabolic disorders by restoring disturbed homeostasis. The reduction in postprandial blood TAG levels after lipid-induced hypertriglyceridemia and modulation of inflammatory cytokines in a situation of induced inflammation depended not only on the fruit extracts but also on the photoperiod of consumption. Specifically, cherry and plum extracts stand out for the control of hypertriglyceridemia when consumed during L6, and winter-fruit extracts and strawberry extract for the prevention of inflammation. Moreover, this research highlights the importance of considering the effects of seasonality of consumption on the effectiveness of phenolic extracts, not only when investigating their biological effects, but also in nutritional interventions, an aspect that has not yet been factored into current nutritional interventions. In addition, these results open the door for the design of novel functional ingredients tailored to each season, with a particular focus on metabolic diseases. By designing food supplements that align with different seasons, it might be possible to provide specific nutritional needs depending on the time of the year and new nutritional approaches for addressing metabolic-related disorders. Further studies are needed to validate the promising potential of these phenolic-rich extracts, including not only clinical trials assessing the bioactive fractions under different photoperiods but also analyses of sensory and consumer

acceptance. Nevertheless, significant research remains to be conducted to understand the mechanisms behind the changes induced by the photoperiod, as well as human studies to validate the effects observed in animal models.

Acknowledgments

The authors thank Niurka Dariela Llópiz and Rosa Maria Pastor for their valuable support and work in the laboratory. F.M. and È.N.M. are recipients of a predoctoral fellowship from the Universitat Rovira i Virgili—Martí i Franquès (Grant numbers: 2019PMF-PIPF-19 and 2019PMF-PIPF-73, respectively). D.M. is a recipient of the grant FJC2020-044585-I funded by MCIN/AEI /10.13039/501100011033 and cofounded by the European Union NextGenerationEU/PRTR. Graphical abstract was created in BioRender. Bravo, F. (2025) https://BioRender.com/f5ed504.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available on request from the authors

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