



Only a matter of time: the impact of daily and seasonal rhythms on phytochemicals

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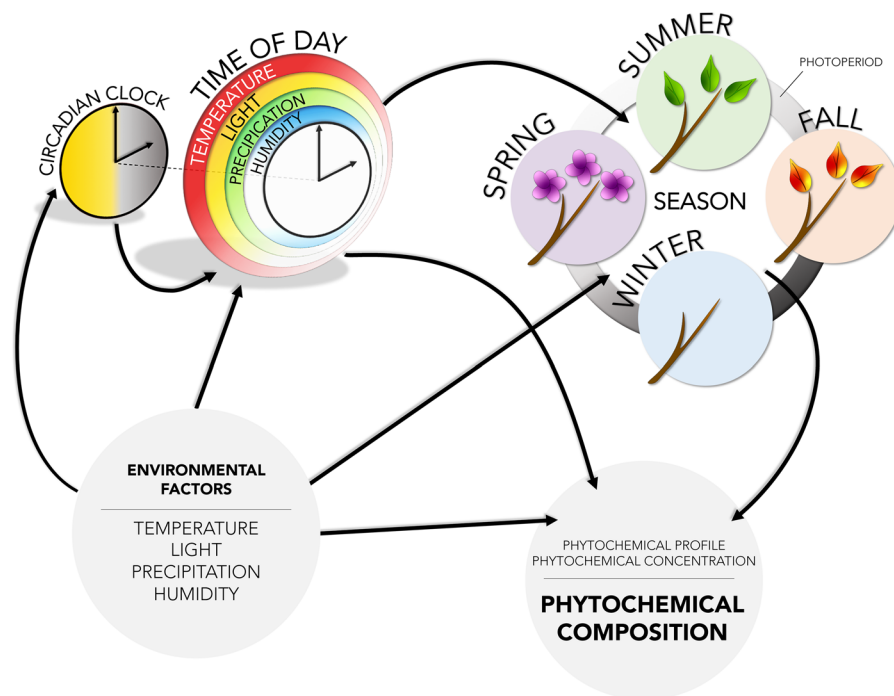


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Abstract Plants regulate molecular bioactivity in response to daily and seasonal environmental fluctuations in temperature, light, humidity, and precipitation. These rhythms interconnect, overlap, and feedback both into each other and into the plant's endogenous circadian clock. The resulting regulatory network tightly ensures that the overall phytochemical composition is highly adaptive to the plant's needs at any point in time. Temporally coordinated control of primary and secondary metabolism ensures phytochemicals are in tune with the demands of the environment and the available resources. As a consequence, phytochemical composition varies throughout the day and year. This variation in phytochemical abundance and composition across time can affect experimental results and conclusions. Understanding how phytochemical composition varies across time is critical for uncovering the underlying regulatory connections and ultimately improving the quality of phytochemical products. Herein, we review the mechanisms underlying diel and seasonal variations in phytochemical composition and provide examples of temporal regulation of specific compounds within phenol, terpenoid, and alkaloid phytochemical classes.

Graphic abstract Temporal regulation of phytochemical composition. The phytochemical composition of a plant is under complex control, affected by both external environmental factors and endogenous circadian rhythms. The environmental factors that directly affect phytochemical profiles and concentrations themselves vary across time of day and time of year. These cyclic environmental factors also entrain the endogenous circadian clock which imposes additional regulation on the production and processing of many phytochemicals. This concerted effort to ensure phytochemicals are exquisitely in tune with the demands of the environment results in fluctuating phytochemical composition. Variation in phytochemical abundance and composition across time can affect experimental results and conclusions. Failing to consider the factors of time of day and year can result in misleading or inconsistent estimations of the potency and composition of phytochemical extractions. Integrating temporal factors will improve our understanding of the underlying regulatory connections and ultimately improve the quality of phytochemical products.

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Introduction

The properties that determine the perceived value of a plant as a source for phytochemicals depend on the composition, relative concentration, and potency of these bioactive molecules. All of these factors can vary as highly plastic plant biochemistry responds dynamically to the environment. Research on specialty crops producing phytochemicals has shown that value-added phenotypes from aesthetics to flavor and texture vary with environmental changes. In turn, these variations can impact shelf life, food safety, and health benefits that determine the value and drive the consumer perception of quality (Ahmed and Stepp 2016). Risks for food waste and financial harm to producers and retailers are enhanced as devalued or unaesthetic products are discarded (Buzby et al. 2014). For example, consumers can taste the difference

between tea leaves grown in the sun versus shade (Ahmed et al. 2010) or harvested during the monsoon season versus the dry spring (Ahmed et al. 2014). Therefore, understanding how environmental factors impact the phytochemical composition can have profound consequences in breeding and agricultural production of specialty crops.

Variation in primary metabolism throughout different times of day or seasons of the year is well-established (Farré and Weise 2012). However, comparatively little is known on the temporal regulation of specialized metabolites. Temporal changes in metabolite concentrations can alter the efficacy of nutraceuticals. Daily or seasonal changes in the metabolic profile of a plant can alter the toxicity or potency. Moreover, understanding the temporal variation in specialized metabolites can improve selection and breeding strategies, increasing the consistency of phytochemical production and research. In this review, we focus on the impact of recurring daily and seasonal cycles on phytochemical biochemistry. We provide a general overview of the mechanisms that can drive daily and seasonal variation in phytochemical levels and then provide specific examples of compounds in various phytochemical classes that show daily and seasonal variation. Finally, we discuss

how current trends are changing these rhythmic environmental patterns and how these changes may impact phytochemical research and production.

In several plant species, the regulatory and biosynthetic genes of specialized metabolite pathways show circadian, diel, or photoperiod driven rhythmic transcript expression (Alabadí et al. 2002; Filichkin et al. 2011; Pavarini et al. 2012; Gyllenstrand et al. 2014; Soni et al. 2015; Fenske and Imaizumi 2016; Zeng et al. 2017; Greenham et al. 2017; Koda et al. 2017; Weiss et al. 2018; Yin et al. 2018; Yoshida and Oyama-okubo 2018). The correlation between changes in transcript and metabolite levels will depend on the environmental conditions and the specific pathway of interest. Therefore, in this review, where possible, we focus on evidence of temporal variation at the metabolite level.

Daily cycles of environmental change drive variation in phytochemical production and processing

Plants coordinate their molecular activities by time to operate at optimum efficiency. Growth, stomatal opening, photosynthesis, metabolism, nutrient, and water uptake are timed to coincide with the availability of resources; primarily light and water (Nozue and Maloof 2006; Harmer 2010). Throughout a 24 h period, there are changes in light intensity, light quality, temperature, and humidity. These four factors have a direct impact on nutrient uptake and photosynthesis and therefore impact the availability and distribution of carbon and nitrogen (Ruffy et al. 1989; Bläsing et al. 2005; Ruts et al. 2012). This cycling availability of carbon and nitrogen starting materials has consequences on the production and processing of specialized metabolites. In addition to modulating the availability of the building blocks necessary to generate specialized metabolites, these daily-changing environmental factors also directly influence the pathways that regulate specialized metabolites. Not only do temperature, humidity, light intensity, and quality directly influence specialized metabolite levels, these four factors also serve as cues to modulate the plant's circadian clock so that it is in sync with the local environment (McClung 2006, 2008; Harmer 2010; Mwimba et al. 2018). This internal circadian clock also regulates the production

and processing of specialized metabolites (Bläsing et al. 2005). Finally, the physiological and molecular responses to abiotic and biotic stresses are 'gated' so that the potential for response is maximal when the stress stimulus is most likely to occur.

Regulation of phytochemicals by changes in light quality and temperature

For many phytochemicals, their accumulation levels are directly affected by changes in light, temperature, and water availability. As these environmental features vary both throughout the day and year, the impact of these environmental variables can result in their altered accumulation depending on the time of day or year the plant is sampled.

Light quality

The filtering effects of the atmosphere change as the position of the sun in the sky changes throughout the day and the year, altering the total light intensity. Additionally, since the atmospheric filtering is not consistent across all wavelengths, this change in the angle of the sun also impacts the spectrum of light that is available to plants. The accumulation of some phytochemicals is directly impacted by changes in light quality, perhaps driving their daily and seasonal variation in levels.

Blue light and other shorter wavelengths are strongly affected by Rayleigh scattering, resulting in a lower abundance of these wavelengths in winter as well as dawn and dusk which leads to an increase in the relative amount of the longer, red wavelengths. The ratio of the red to far-red wavelengths impacts developmental transitions such as the transition to flowering. The mechanism for this sensitivity in *Arabidopsis* is through the light-quality dependent switching of the phytochromes between active and inactive states (Ulijasz and Vierstra 2011; Ushijima et al. 2017; Sethe et al. 2017). The phytochromes in *Arabidopsis* impact photosynthesis and primary metabolism (Yang et al. 2016a, b; Kreslavski et al. 2018). Loss of phytochromes alter the metabolic profiles with increases in sugars and amino acids. These changes are similar to those observed in plants under abiotic stress, in particular, there is a large accumulation of proline and raffinose (Yang et al. 2016a, b). Transcriptional responses to stress are also induced in the

phytochrome mutants, suggesting a connection between light quality sensing through the phytochromes and induction of abiotic stress responses.

Several phytochemical pathways are sensitive to changes in light quality. Both red and blue light enhance total antioxidant activity in the Chinese medicinal herb, *Rehmannia glutinosa* (Manivannan et al. 2015). Total phenol content and flavonoid levels were responsive to specific wavelengths. Blue-light resulted in higher phenol content while red-light favored an increase in flavonoid levels. Red light induction of flavonoids was also reported in *Pisum sativum* (Bottomley et al. 1966). However, in other species, flavonoid levels increase with blue light. In the medicinal plant, *Cyclocarya paliurus* total flavonoid levels were the most responsive to blue light (Liu et al. 2018). The levels of the flavonoids quercetin and 3-malonylglucoside and the phenylpropanoid cichoric acid increase under prolonged enhanced blue light in red leaf lettuce and basil (Taulavuori et al. 2016). In *Betula pendula* (silver birch) seedlings, UV-B supplementation also increased levels of quercetins, kaempferols, and chlorogenic acids (Tegelberg et al. 2004). Total essential oils increased under blue and red light in *Mentha piperita*, *M. spicata*, and *M. longifolia* compared to white light or sunlight (Sabzalian et al. 2014). However, like flavonoids, the effect of light quality on essential oils tends to be species specific. In the Sabzalian et al. (2014) study, the three *Mentha* species showed significantly higher levels of essential oils under red light compared to blue light. Red light also increased menthol levels, the primary essential oil compound in *Mentha arvensis*, greater than blue light (Nishioka et al. 2008). In *Mentha piperita*, menthol biosynthesis was reduced by 25% when supplemented with blue light and resulted in a significant decrease in essential oil and total phenol content (Maffei and Scannerini 1999). A recent review by Dou et al. (2017) provides other examples of light quality impacts on phytochemicals in herb species. The seasonal changes in light quality are greatest the farther one is from the equator suggesting that there will be an interaction between seasonal variability and latitude.

Temperature

The variation in temperature throughout the year, particularly in temperate climates, can be quite drastic.

Perhaps less obvious is that the day to night temperature differential can also be significant, even in tropical climates. This variation in temperature across time of day and season of the year can also result in a corresponding variability in phytochemical levels. Total glucosinolate levels and ascorbic acid increased in sprouts germinated at 30 °C compared to those at 20 °C or 10 °C in broccoli (*Brassica oleracea*) and rocket sprouts (*Eruca sativa*) (Ragusa et al. 2017). Increasing temperature enhanced the total polyphenol content of broccoli sprouts but reduced the total polyphenol amount in rocket sprouts. Increasing temperature (20 °C, 25 °C, and 30 °C) also resulted in significantly greater phenolic acid and flavonoid production in wheat (*Triticum* spp.), irrespective of genotype (Shamloo et al. 2017). The levels of campesterol decreased across genotypes while other phytosterols in wheat were not significantly affected by the temperature change. In St. John's wort (*Hypericum perforatum*) 15 days of elevated temperature (30 °C or 35 °C) before harvest increased the concentration of the anthraquinones, hypericin and pseudohypericin, and the phloroglucinol, hyperforin (Zobayed et al. 2005). These are considered the active compounds in *H. perforatum* (Bauer et al. 2001) and their sensitivity to temperature may result in different potency for harvested plant material.

In *Zea mays* (Christie et al. 1994), Arabidopsis (Leyva et al. 1995; Rowan et al. 2009), *Nicotiana tabacum* (Huang et al. 2012) and apple (*Malus* spp.) (Ubi et al. 2006) anthocyanin levels are increased by lower temperatures and reduced in higher temperatures. Changes in phytochemical levels in response to temperature are dynamic processes and evaluating the response to temperature at a single time point may not provide a clear picture of the full intersection between the changing temperature and the biochemical response. For example, in plum fruit (*Prunus salicina*) the initial response to high temperature is an increase in anthocyanin, however, after 9 days at high temperatures, the total anthocyanin dropped below control levels (Niu et al. 2017). Monitoring the activity of a hydrogen peroxide-based degradation mechanism showed that the accumulation of anthocyanin is a balance between synthesis and degradation. The reactive oxygen-based degradation suggests other environmental factors may modulate the temperature-induced degradation of anthocyanin in plum fruit.

Changes in temperature are not uniform, the plant response to temperature changes at night are distinct from temperature perturbations during the day (Grinevich et al. 2019). The difference between day and night temperature impacts the overall growth of tomato (*Lycopersicon esculentum*), fruit quality, and the secretion of low molecular weight organic acids from the root which can impact nutrient uptake (Papadopoulos and Hao 2000; Yang et al. 2014, 2016a, b). A mild increase in nighttime temperature appears to impact primary metabolism resulting in reduced yield and grain quality in rice and wheat (Ziska and Manalo 1996; Peng et al. 2004; Counce et al. 2005; Lobell and Ortiz-Monasterio 2007; Kanno et al. 2009; Mohammed and Tarpley 2009; Welch et al. 2010; Glaubitz et al. 2015; Laza et al. 2015; Shi et al. 2017; Impa et al. 2018). An enrichment for stress-responsive and reactive oxygen scavenging proteins was observed specifically under increased night temperatures in rice grains (Li et al. 2011). If these altered changes occur in other plant species, the impacts of changes in night temperature on specialized metabolites could be distinct from the impacts of changes in temperature during the day. Most studies to date investigate the response of specialized metabolites to increasing temperatures by employing higher daytime temperatures or a consistent increase in both day and night temperatures. The asymmetric pattern of global warming (IPCC 2018; Xia et al. 2014) suggests that it will be essential to understand the impacts of warming nights on specialized metabolite production. Ibrahim et al. (2010) investigated the specific role of altered night temperatures on volatile organic compounds (VOCs) and found that increasing night temperatures increased the VOC emissions detected during the day. Most VOCs examined showed a linear relationship between increasing night temperature and emission levels. However, in contrast to previous studies that examined daytime temperature changes, isoprene emission was not correlated with rising temperatures at night (Gouinguene and Turlings 2002; Tarvainen et al. 2005; Helmig et al. 2007; Sharkey et al. 2008; Copolovici et al. 2012). The VOC isoprene may provide an adaptive role (Sharkey et al. 2008) protecting plants from heat-induced damage, (reviewed in Sharkey et al. 2008). Therefore, understanding if isoprene emission is differentially responsive between night and day temperatures could

impact our understanding of how the perception and response to stress vary across time.

Water availability

For most plants, the availability of water varies daily and seasonally. Diel oscillations in water potential in the plant are driven by active photosynthesis and associated transpiration through open stomata during the day. At dawn the humidity drops and simultaneously stomata open, resulting in increased water losses from aerial plant tissue (Klepper 1968). The water potential continues to drop throughout the day as the open stomata facilitate CO₂ acquisition. In most species, water potential is the lowest in the late afternoon. Once the stomata close, the rate of water uptake exceeds the rate of water loss and leaves and fruits regain their water potential. In some plant species, the increased water potential at night fuels the hydraulic redistribution of moisture in the soil (Richards and Caldwell 1987; Caldwell et al. 1998). This daily rhythm persists even with reduced water levels. Low water potential in the root environment, through loss of soil moisture throughout the daytime period, can impact nutrient uptake and the transport of metabolites or the precursors needed to generate phytochemicals (Plaut and Reinhold 1965; Greenway et al. 1969).

Changes in water availability throughout the year have a higher amplitude than daily changes. In most locations, precipitation and water availability have a strong seasonal component with a wet and dry season (Snyder and Tartowski 2006; Taxak et al. 2014). Water availability affects the accumulation of several phytochemicals. In *Coffea arabica* leaves, irrigation reduced the levels of the quinone pheophytin, a photosynthetic pigment (Scheel et al. 2016). Tea (*Camellia sinensis*) harvested during the dry season had higher concentrations of desirable methylxanthines and polyphenols than in the monsoon season (Ahmed et al. 2014). Phenolic accumulation in response to drought has also been reported in *Amaranthus tricolor* (Sarker and Oba 2018) and *Zea mays* (Hura et al. 2008). However, phenolic content shows variability in response to water availability across plant species. In peanut (*Arachis hypogaea* L.), phenolic content increased in leaves and stems in response to drought stress, but decreased in the seeds (Aninbon et al. 2016). Using a rain-out shelter

Cheruiyot et al. (2007) observed that tea cultivars had lower phenolic levels in drought conditions. A similar decrease in phenolic content was observed in cotton leaves (Shah et al. 2011; Shallan et al. 2012), and under progressive water deficit, both Shiraz and Cabernet Sauvignon grape cultivars (*Vitis vinifera*) showed a decrease in flavonols and non-flavonoid phenolic compounds (Hochberg et al. 2013). In the Shiraz cultivar, quercetin-3-*O*-galactoside and rutin increased under water deficit. Phenolic compounds decreased in response to drought in sensitive tomato (*Solanum lycopersicum* L.) cultivars, but increased in response to drought in Zarina, a tolerant cultivar (Sánchez-Rodríguez et al. 2011). The tolerant Zarina cultivar also showed an increase in rutin and flavonoid levels. In other plant species drought induces the accumulation of flavonoids (Hernández et al. 2004; Yang et al. 2007; Ma et al. 2014; Shojaie et al. 2016). Under mild drought stress, the diel accumulation patterns of non-structural carbohydrates showed stress-induced changes in *Brassica rapa* plants, suggesting an interaction between diel regulation and abiotic stress responses (Greenham et al. 2017).

Under both mild and moderate water stress the components of essential oils, geraniol, and citral increased in two species of lemongrass, *Cymbopogon nardus* and *Cymbopogon pendulus* (Singh-Sangwan et al. 1994). In medicinal plants, the concentration of desired phytochemicals can be increased by growth in water limiting conditions (Jaafar et al. 2012; Selmar and Kleinwächter 2013). For example, the accumulation of hyperforin in St. John's wort (*Hypericum perforatum*) (Zobayed et al. 2007) and ajmalicine in *Catharanthus roseus* (Jaleel et al. 2008) increases in response to reduced water stress.

Like changes in the pattern of temperature cycles, climate change is affecting the timing of precipitation events, with a seasonal component to even extreme precipitation events (Unal et al. 2012; Pal et al. 2013; Keggenhoff et al. 2014; Ganguli and Ganguly 2016; Gitau 2016; Rahimpour et al. 2016; Tye et al. 2016; Mallakpour and Villarini 2017; Roque-Malo and Kumar 2017). In the US Ohio/Missouri River valleys, the start of the dry season is altered by 2–3 weeks while the wet season in east New York arrives about 3 weeks earlier than a century ago (Pal et al. 2013). These disruptions to the seasonal patterns of water availability may alter the phytochemical composition

of plants even if they are harvested at the same time of year.

Additional examples of the effects of light, temperature, water availability and other environmental factors on the accumulation of specialized metabolites have been reviewed by Ramakrishna and Ravishankar (2011), Ncube et al. (2012), Verma and Shukla (2015), Borges et al. (2017), Yang et al. (2018).

Regulation of phytochemicals by the circadian clock

The plant's endogenous circadian clock is a crucial part of coordinating molecular activities with resource availability that varies daily and seasonally, thereby providing an evolutionary advantage (Green et al. 2002; Dodd et al. 2005; Yerushalmi et al. 2011; Bendix et al. 2015). Most of the evidence for diel variation in metabolism and environmental responses is inferred from transcriptional patterns of expression that show rhythmic diel- or circadian-driven patterns of expression (Alabadi et al. 2002; Bläsing et al. 2005; Michael et al. 2008; McClung 2014). The comparatively straightforward ability to measure transcripts levels enabled the evaluation of daily rhythmic expression patterns across various plant species. However, protein and metabolite levels also show daily rhythmic patterns of accumulation (Gibon et al. 2006; Graf et al. 2010; Hwang et al. 2011; Flis et al. 2016). In the model plant *Arabidopsis*, both primary (e.g., maltose, fructose, GABA, and isoleucine) and specialized metabolites (e.g., flavonoids and terpenoids) show a daily oscillation in their abundance (Aharoni et al. 2003; Stitt et al. 2007; Espinoza et al. 2010; Augustijn et al. 2016). Once entrained, the accumulation of some specialized metabolites shows a rhythmic pattern in the absence of light, temperature, or humidity cues indicating that this pattern of accumulation is under the control of the circadian clock (Gibon et al. 2006). Disruption of the circadian clock significantly alters metabolism, including levels of specialized metabolites (Fukushima et al. 2009).

Gating of environmental responses

Many biotic stressors such as bacterial and fungal pathogens and herbivores (Hevia et al. 2015) have a daily rhythm to their activity. Additionally, many abiotic stresses have an increased probability of

occurring at a specific time of day or season. Plant responses to these environmental stresses are temporarily coordinated. This ‘gating’ ensures that the stress response is maximal at the time that coincides with the highest probability of the stress occurring. Circadian control of signaling occurs in part through gating the response to phytohormones such as auxin, abscisic acid, jasmonic acid, and salicylic acid (Covington et al. 2008; Goodspeed et al. 2012).

Arabidopsis plants show decreased susceptibility to the pathogens *Pseudomonas syringae* pv. *tomato* DC3000 (Bhardwaj et al. 2011) and *Botrytis cinerea* (Ingle et al. 2015) at dawn. Even basal defense mechanisms are under circadian control (Wang et al. 2011) suggesting that this is not a unique aspect of these two pathogens. Interaction with beneficial species such as attraction of pollinators and parasitoids must also be coordinated with the daily rhythms of these insects. The emissions of the primary mediator of this attraction, volatile organic compounds (VOCs), show variation throughout the day. For example, fig (*Ficus racemosa*) volatiles can be distinguished by their diel variation in temporal patterns (Borges et al. 2013). At any given point in the day, the fig plants present a different volatile profile to match with the biological activity of the parasitoids and pollinators.

Deleterious insects also show rhythmic behaviors and many of the plant responses to herbivory are gated to match the activity of the herbivore. A large percent of metabolites induced by generalist herbivores peak in accumulation at specific times of the day. For example, *Nicotiana attenuata* has a diel rhythm of jasmonic acid (JA) and 12-oxo-phytodienoic acid (OPDA) accumulation in roots, but not in leaves (Kim et al. 2011). The metabolites that oscillate in the shoots, such as citric acid, tyrosine, phenylalanine, and lyciumoside, were mostly found to peak during the day. In contrast, the metabolites that oscillate in roots, such as disaccharides and JA mostly peak at dusk or at night. The biosynthesis of these metabolites is also tissue-specific. Lyciumoside which is a precursor to diterpene glycosides, peaks at dusk and is more prevalent in sink leaves than in source leaves. The circadian gating of the response to herbivory alters the interaction between the plant and the herbivore. *Trichoplusia ni*, a cabbage looper insect, show rhythmic feeding behavior that peaks in the afternoon (Goodspeed et al. 2012). *Arabidopsis* plants are able to defend against the *T. ni* herbivory through concerted

timing of jasmonate production and simultaneous reduction in salicylates. However, disruption of the plant circadian clock or switching the phase of *T. ni* feeding reduces these defenses. Like jasmonates and salicylates, many phytochemicals have a role in plant defenses. Thus this gating of defense responses, combined with the effects of daily rhythms in primary metabolism, environmental and circadian regulation of specialized metabolite biosynthesis and processing likely drive significant variation in phytochemical levels throughout the day.

The response to abiotic stresses of temperature (Fowler et al. 2005; Dong et al. 2011; Grinevich et al. 2019), UVB (Takeuchi et al. 2014; Horak and Farré 2015), and reactive oxygen species (Lai et al. 2012) are also gated so that the response varies throughout the day. The master regulators of low-temperature responses, CBF transcription factors, show the highest response to a 4 °C cold shock in the morning and a reduced induction in response to the same stress at night. The CBFs control, in part, the rewiring of metabolism that occurs under low temperature (Cook et al. 2004). In Arabidopsis, metabolism is significantly rewired at low temperature (4 days at 4 °C), including induction of phenylpropanoid levels (Kaplan et al. 2007). Constitutive expression of CBF3 recapitulates 79% of the metabolic changes observed under low temperature in control conditions (Cook et al. 2004). Since the response of CBF3 to low temperature is gated by the circadian clock, the induction of the low-temperature-responsive metabolites regulated by CBF3 is also likely gated.

Seasonal changes

Perhaps more drastic than daily changes, environmental factors vary in seasonally-recurring patterns including changes in precipitation, temperature, and day length. Biotic and abiotic stresses also show seasonal variation in their probability of occurrence. In addition to these exogenous changes, as a plant develops throughout the season there are developmentally-regulated changes in phytohormones auxin, gibberellin, ethylene, and jasmonates that interact with environmental changes altering the sensitivity of the plant to different stimuli depending on the time of the season (Davies 2010; Footitt et al. 2011; Singh and Mas 2018).

Photoperiod

Both north and south of the equator there is an asymmetry to the amount of light or day length throughout the year. The amplitude of the difference between the long days of summer and the shorter days of winter increases with the distance from the equator. Seasonal changes in photoperiod are concomitant with seasonal changes in light intensity and temperature. Therefore, when isolating the factor of photoperiod, chamber-based experiments comparing different day lengths are often performed. One challenge with these experiments is that the chamber-experiments are often performed with square waves where the changes in light intensity and light quality which also vary across the day and season are ignored. Ignoring these subtle changes can result in missing important mechanisms that control for the integration of signals (Liao et al. 2017). Most plant species are sensitive to changes in photoperiod and respond by adjusting growth and developmental stages. For example, silver birch, *Betula pendula*, integrates both temperature and photoperiod cues to control the timing of bud burst (Linkosalo and Lechowicz 2006). The chilling requirement is met long before the modeled initiation date, suggesting a second cue is integrated to control the timing of bud burst. Linkosalo and Lechowicz compared the effects of a reduced red to far-red ratio throughout the day or only at dawn and dusk and demonstrated that the diurnal timing of the change in light quality is an important factor in this developmental transition. The integration of both light quality timing and temperature changes may protect some species from frost damage due to early budding associated with warm early-spring weather. These developmental changes can impact phytochemical composition and distribution in the plant (Degu et al. 2014; El Senousy et al. 2014). For example, in cherry radish (*Raphanus sativus* L. var. 'Changfeng') increase in polyphenol and antioxidant content increased in the root, but not in the shoot when grown in a longer day period (Guo et al. 2019). Photoperiod changes impact the flavonoid, phenolic, amino acid, anthocyanin, alkaloid, and glucosinolate levels (Bernarth and Tetenyi 1979; Xu et al. 2011; Steindal et al. 2015). Phytochemical responses to photoperiod have been reviewed in Verma and Shukla (2015). In addition to these general impacts on phytochemicals, for many compounds, specific response to photoperiod

have been described. We highlight below some examples, grouped by chemical class, of phytochemicals where the daily and seasonal variation has been described (Table 1).

Examples of daily and seasonal variation on specific phytochemicals

Polyphenols and phenolic compounds

Polyphenols are generally high molecular weight molecules derived from the shikimate, phenylpropanoid, flavonoid, anthocyanin, lignin (Mouradov and Spangenberg 2014) and polyketide pathways in plants. A large number of phenolic hydroxyl groups provide these compounds with unique metabolic properties and compounds in this class have a range of functions *in planta* including UV protectants, defense compounds, signaling molecules, antimicrobials, and antioxidants. Polyphenols have been confirmed as the source of biological activity in many medicinal plants, particularly those used to prevent and ameliorate metabolic diseases (Cvejić et al. 2017; Chen et al. 2018).

Circadian, diel, and seasonal effects on total polyphenols

The regulatory and protective functions of phenols in oxidative stress-induced signaling may explain the observed rhythmic accumulation in many plant species. In *Arabidopsis*, the response to reactive oxygen is circadian regulated (Lai et al. 2012). Consistent with this observation, antioxidant activity was found to be circadian regulated in other *Brassica* (Soengas et al. 2018). However, the temporal signature of antioxidant activity was not consistent across diverse species. Coordinating antioxidant activity with the recurring timing of local stresses, other phenological activity, or breeding pressures could drive species-specific changes in the waveform of expression that could be locally adaptive. Soengas et al. observed circadian driven rhythmicity in the pattern of total phenolic compound accumulation in broccoli, cabbage, Chinese cabbage, and turnip greens. Although all species accumulated the highest total phenolic content in the period surrounding dawn, the specific phasing of the peak in accumulation varied between

species. Broccoli and cabbage accumulation was the highest in the dark period before dawn while Chinese cabbage and turnip greens peaked in accumulation at dawn. Specific compounds also showed variability in their waveform of selection discussed below. Selection for desired traits or the need to meet the pressures of local environments may result in observed altered temporal profiles between species. We provide examples below for where the time of day and season of year variation in accumulation has been observed for polyphenolic compounds.

Flavonoids

Flavonoids function as pigments, signaling molecules, UV-protectants, and antimicrobials. Daily rhythms of flavonoids have been reported in the tropical tree, *Anacardium excelsum* and the fern, *Cryptogramma crista* (Veit et al. 1996). In grape berries, (*Vitis vinifera*) (Reshef et al. 2019) the diel pattern of expression for some flavonoids was sensitive to the orientation of the berry in relationship to the sun. The flavonoid quercetin showed a rhythmic accumulation in all three orientations. However, other flavonoids, such as cyan-3glu, were rhythmic in some positions but showed no change in signal across the day in others. The observable difference in flavonoid accumulation in response to the small change in solar irradiation due to the position of the berry relative to the large daily oscillatory light suggests that the sensitivity of the phytochemical response is attuned to account for this daily change in light intensity. Seasonal variation in anthocyanin levels can manifest if the plant is harvested at different times of the year. For, strawberry fruit (*Fragaria x ananassa*), plants at the same ripening stage and harvested at different times of the year showed variation in anthocyanin accumulation levels (Pincemail et al. 2012; Ariza et al. 2015). Strawberries harvested earlier in the year had the lowest content of organic acids and antioxidant compounds, perhaps indicating a role for increasing day length in the accumulation of these phytochemicals (Ariza et al. 2015). Over all genotypes, strawberries in the mid to late harvest showed overall better health-related properties. There was an interaction between cultivar and the compound time of harvest suggesting that healthy harvesting could be achieved by staggering plantings by cultivar and should be a factor considered during breeding selection.

Phenylpropanoids, phenolic acids, and aldehydes

Both the time of day and time of season plants are harvested can impact the phenolic acid content for some plant species. Broccoli head (*Brassica oleracea* L.) harvested at the end of the day had higher phenolic content and antioxidant activity during storage than those harvested in the morning or at midday (Hasperué et al. 2011). The time of year plants are harvested can impact the nutritional quality of the product as much as the genotypic variation. Four different cloudberry (*Rubus chamaemorus*) genotypes were examined throughout the year and seasonal variations were observed in gallic acid, ellagic acid, and anthocyanins (Hykkerud et al. 2018). Across all genotypes, cloudberry plants harvested early- and mid-season contained significantly higher ellagic acid levels than those harvested in late season (7.41, 7.03 and 6.35 mg/g dry weight, respectively). This pattern reflected the total phenol measurement, which was on average higher in early-season, decreasing in mid- and late-season (22.12, 20.97, 20.09 mg/g dry weight, respectively). Although the variation between genotype was more significant than the seasonal variation, ellagic acid was still significantly responsive to environmental variation. In an earlier study in *Rubus* species, raspberry fruits (*Rubus idaeus*), Mazur et al. (2014) compared ten genotypes of raspberry fruit for the effects of harvest season and genotype on phenolics, ellagic acid, anthocyanins, and ascorbic acid content. Only ascorbic acid content was consistent across harvest seasons. Phenolics, ellagic acid, and anthocyanins showed significant variation depending on the time of year the berries were harvested. The study concluded that the “Quality of red raspberry fruits were significantly affected both by genotype and harvest season.”

Total phenolic content and phenolic profile varied in globe artichoke [*Cynara cardunculus* L. var. *scolymus* (L.) Fiori] between plants harvested in the winter or spring (Lombardo et al. 2010). The phenolic content increased sixteen times in the later spring harvest. Several compounds, 1- and 3-*O*-caffeoylquinic acids, caffeic acid, narirutin, and naringenin 7-*O*-glucoside were only detected in the spring harvest, changing the overall polyphenol profile. The variation in total phenolic content of *Vochysia divergens* Poh., a pioneer tree species was greater across the season that between geographic areas in Brazil (Uriu

et al. 2018). Harvest time also affected the total level of phenols and antioxidant activity in grape cultivars (*Vitis vinifera*) (Piazzolla et al. 2016). In this study, the harvest time of grapes was also found to influence the distribution of volatiles including acetaldehyde, 2-butenal, hexanal, ethyl acetate, ethanol, D-Limonene resulting in an overall change in grape quality. In the Piazzolla et al. study, since the grapes were not at the same developmental stage, the effect observed is likely a combination of developmental and environmental effects.

Hydroxycinnamic acids

Leaf oils showed a time of day and time of year variation in *Lippia origanoides* Kunth (Ribeiro et al. 2014). Examining plants collected near a mine in Brazil, Ribeiro et al. identified many metabolites with significant variation throughout the year. The major specialized metabolites with a time of year change in concentration were (E)-methyl cinnamate, (E)-nerolidol, p-cymene, 1,8-cineole, carvacrol, α -pinene, (E)-caryophyllene and g-terpinene. Cinnamate levels also varied by time of year with no accumulation from March through June, followed by moderate accumulation in July, peaking in concentration in August, and returning to moderate levels from September through February. Cinnamate also showed significant variation in concentration depending on the time of day samples were harvested.

In kimchi [green Chinese cabbage (*Brassica rapa*) and red cabbage (*Brassica oleracea*)], fall and spring-sown cultivars were compared for two genotypes. The phenols caffeic acid, p-coumaric acid, ferulic acid, and sinapic acid and flavonols (quercetin and kaempferol) showed significant differences in levels between fall and spring in both red cabbage cultivars tested (Lee et al. 2018).

Naphthoquinones and quinones

The medicinal plant, *Euclea undulata* produces epicatechin and α -amyrin-3O- β -(5-hydroxy) ferulic acid, both desired for their potential value in the treatment of diabetes. However, *E. undulata* also produces the naphthoquinone, 7-methyl-juglone, which is cytotoxic. Botha et al. (2018) evaluated the environmental and seasonal effects on the accumulation of these three compounds to determine if altering the harvest time

could eliminate the presence of 7-methyl-juglone. Comparing plants harvested in the rainy (December) and dry (August) season, in three locations, they observed both geographic and seasonal effects on the metabolite profile. While the variation in metabolites between geographic locations was greater than the variation between seasons, at a given location, seasonal differences had a significant impact on the metabolic profile. In particular, the 7-methyl-juglone was not detectable in leaves in the rainy season in the summer rainfall region, while plants from the same region accumulated 7-methyl-juglone in the dry season. In this same region, the desired compounds epicatechin and α -amyrin-3O- β -(5-hydroxy) ferulic acid, also showed seasonal variation and the stems and leaves of *E. undulata* Thunb. var. *myrtina* contained both epicatechin and α -amyrin-3O- β -(5-hydroxy) ferulic acid and lacked 7-methyl-juglone only in the rainy season. Therefore, the authors concluded, “For the safe and effective use of *E. undulata* it would be best to collect leaf material during the dry season in the summer rainfall areas.” This example highlights the importance of considering not only the temporal profile of the phytochemicals of interest but also the temporal profile of any negative or even synergistic compounds (e.g., Fig. 1).

Alkaloids

While we found few published studies examining the circadian, diel, or seasonal changes of the alkaloid plant compounds, some evidence exists for diurnal fluctuations of quinolizidine alkaloids (QA) in species in the *Lipinus* genus. The fluctuations of QA concentrations are the greatest in the middle of the day, and these compounds have been found in the phloem of plants and therefore may be translocated to target tissues where their nitrogen is used in the synthesis of storage proteins (Wink and Witte 1984). However, QAs can also be toxic to vertebrate herbivores, and therefore the increase in concentrations observed could be a defense mechanism (Sharam and Turkington 2005). For example, in both *L. polyphyllus* and *L. hartwegii* sparteine increases in the day, while in *L. articus* an increase sparteine is observed at night (Sharam and Turkington 2005). Snowshoe hare are nocturnal and a herbivore of *L. articus*, therefore the night increase in sparteine observed in this species may be for defense.

Fig. 1 Time of day and season of the year impact the composition and abundance of phytochemical extracts. Extract composition quality is a combination of the relative concentration of the phytochemical of interest and the antagonistic or synergistic effects of the remaining profile. Time of day and seasonal variations in the target metabolite, toxins, and synergistic metabolites can be taken into consideration to determine the optimal growing season and time of day to harvest extracts. In the simplified graphic above an extract with the patterns shown would be optimally harvested during the middle of the day to account for diel variations. Harvesting in the summer would provide the maximum efficacy at the lowest toxicity across the yearly seasonal variation

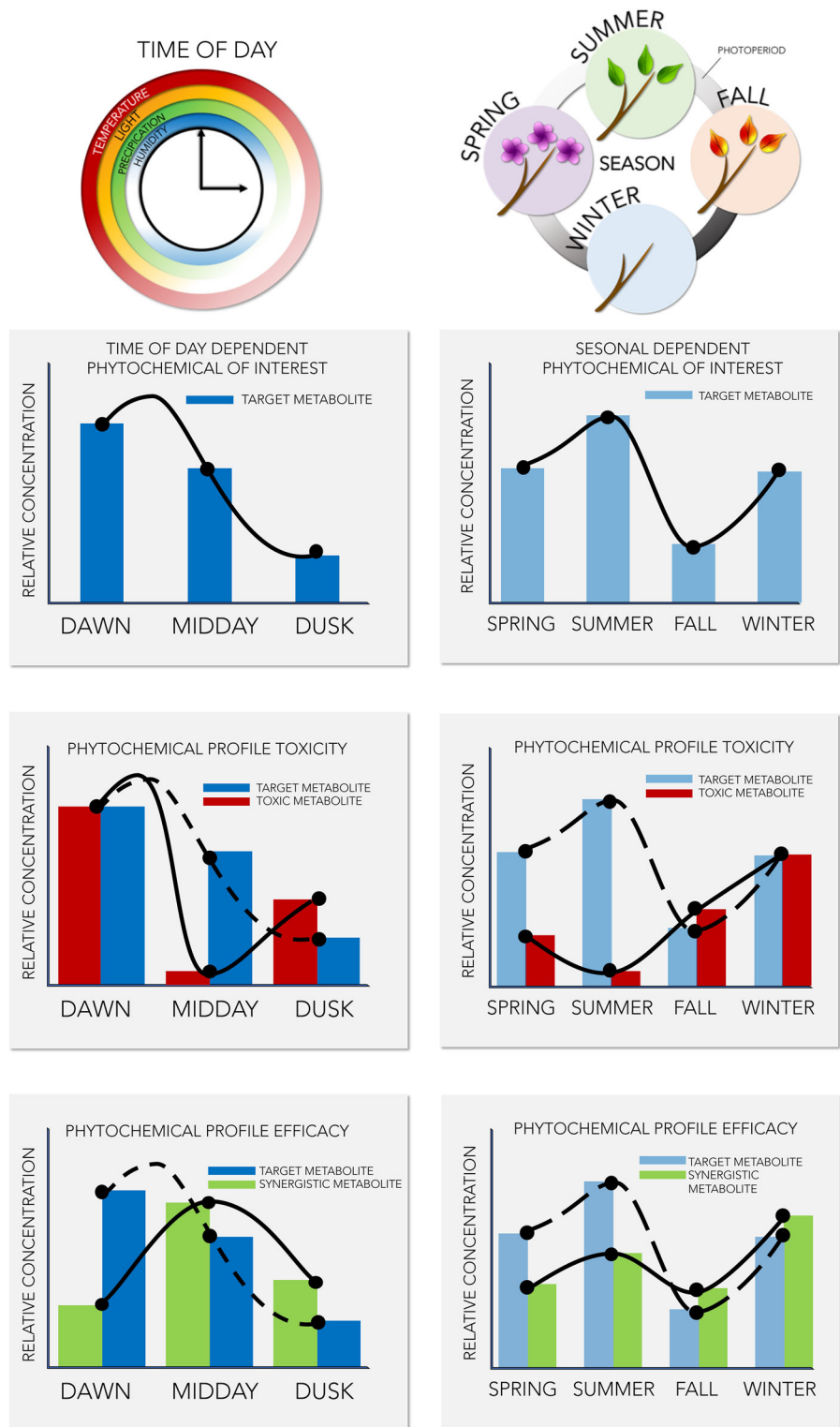


Table 1 Examples of phytochemicals with accumulation that is impacted by the time of day or season. For each class, example compounds that show daily or seasonal variations in levels are indicated in the Diel and Seasonality columns respectively. Phytochemicals with levels controlled by the circadian clock, light, or temperature are indicated. The superscript next to the compound in each row indicates the associated reference describing the variability of the compound

Class	Diel	Circadian	Seasonality	Light	Temperature	References
Alkaloid	Sparteine ^a , Lupinine ^b , Morphine ^d		Ajmalicine ^c			a. Sharam and Turkington (2005) [arctic lupine (<i>Lupinus arcticus</i>)] b. Wink and Witte (1984) [lupine (<i>Lupinus albus</i>)] c. Jaleel et al. (2008) [madagascar periwinkle (<i>Catharanthus roseus</i>)] d. Fairbairn and Suwal (1961) [hemlock (<i>Conium maculatum</i>)]
Naphthodianthrone			7-methyl-juglone ^b		Hypericin ^a , Pseudohypericin ^a	a. Zobayed et al. (2005) [St. John's wort (<i>Hypericum perforatum</i>)] b. Botha et al. (2018) [<i>Euclaea undulata</i>]
Flavonoid	Quercetin ^d	Kaempferol ^b	Kaempferol ^c , Quercetin ^e , Anthocyanins ^{g,h,p,q,r} , Kaempferol ^f , Cyanadin-3-O-glucoside ^b , Naringenin ^s , Quercetin-3-O-galactoside ^q , naringenin 7-O-glucoside ^s	Kaempferol ^{d,e} , Isoquercitrin ^{d,e} , Quercetin ^{d,e,f,g} , 3-malonylglucoside ^f	Rutin ^a , Anthocyanins ^{i,j,k,l,m,n}	a. Shamloo et al. (2017) [wheat (<i>Triticum</i> spp.)] b. Soengas et al. (2018) [cabbage and broccoli (<i>B. Oleracea</i>) Chinese cabbage and tumip greens (<i>B. Rapa</i>).] c. Lee et al. (2018) [Chinese cabbage (<i>brassica rapa</i>)] d. Liu et al. (2018) [light quality; <i>Cyclocarya paliurus</i>] e. Tegelberg et al. (2004) [silver birch (<i>Betula pendula</i>)] f. Taulavuori et al. (2016) [red leaf lettuce (<i>Lactuca sativa</i>)] g. Hykkerud et al. (2018) [cloudberry (<i>Rubus chamaemorus</i>)] h. Mazur et al. (2014) [red raspberry (<i>Rubus idaeus</i>)] i. Christie et al. (1994) [corn (<i>Zea mays</i>)] j. Leyva et al. (1995) [<i>Arabidopsis thaliana</i>] k. Rowan et al. (2009) [<i>Arabidopsis thaliana</i>] l. Huan et al. (2012) [tobacco (<i>Nicotiana tabacum</i>)] m. Ubi et al. (2006) [apple (<i>Malus</i> spp.)] n. Niu et al. (2017) [plum fruit (<i>Prunus salicina</i>)] o. Hochberg et al. (2013) [grape (<i>Vitis vinifera</i>)] p. Reshef et al. (2018) [grape (<i>Vitis vinifera</i>)] q. Pincemail et al. (2012) [strawberry (<i>Fragaria x ananassax</i>)] r. Ariza et al. (2015) [strawberry (<i>Fragaria x ananassax</i>)] s. Lombardo et al. (2010) [artichoke (<i>Cynara cardunculus</i>)]

Table 1 continued

Class	Diel	Circadian	Seasonality	Light	Temperature	References
Glucosinolates			Glucobriferin ^a , Glucoraphanin ^a , Glucobrassicin ^a , 4-hydroxy-glucobrassicin ^a , Neo-glucobrassicin ^a		Glucobriferin ^a , Glucoraphanin ^a , Glucobrassicin ^a , 4-hydroxy- glucobrassicin ^{a, b} Neo-glucobrassicin ^a , glucoerucin ^b	a. Møllmann et al. (2015) [photoperiod; broccoli (<i>Brassica oleracea</i>)] b. Ragusa et al. (2017) [broccoli (<i>Brassica oleracea</i>), rocket sprouts (<i>Eruca sativa</i>)]
Phenylpropanoid	Cinnamate ^a		Cinnamate ^a , P-coumaric acid ^b , Ferulic acid ^{b,d} , Sinapic acid ^b	Cichoric acid ^c		a. Ribeiro et al. (2014) [<i>Lippia origanoides</i> Kunth] b. Lee et al. (2018) [Chinese cabbage (<i>Brassica rapa</i>)] c. Taulavuori et al. (2016) [red leaf lettuce (<i>Lactuca sativa</i>)] d. Botha et al. (2018) [<i>Euclea undulata</i>] a. Sharkey et al. (2008) [review] b. Zobayed et al. (2005) [St. John's wort (<i>Hypericum perforatum</i>)] c. Kim et al. (2011) [tobacco (<i>Nicotiana attenuata</i>)] d. Asghari et al. (2014) [<i>Pycnocycla spinosa</i>]
Terpene	Lycimioside f ^e Citronellyl Pentanote ^d , Geranyl Isovalerate ^d				Isoprene ^a , hyperforin ^b	
Monoterpene	B-pinene ^c , P-cymene ^h	Myrcene ^a	a-pinene ^{b,i} , P-cymene ^b , 1,8-cineole ^b , Carvacro ^l , Germol ^f , Limonene ^{g,i} , g-terpinene ^b , β-pinene ⁱ , Sabinene ^j , myrcene ^j	Menthol ^{l,e}		a. Dudareva et al. (2005) [snapdragon (<i>Antirrhinum majus</i>)] b. Ribeiro et al. (2014) [<i>Lippia origanoides</i> Kunth] c. Lu et al. (2002) [sweet wormwood (<i>Artemisia annua</i>)] d. Nishioka et al. (2008) [<i>Mentha</i> spp.] e. Maffei and Scannerini (1999) [<i>Mentha piperita</i>] f. Singh-Sangwan et al. (1994) [lemon grass (<i>Cymbopogon</i> spp.)] g. Piazzolla et al. (2016) [grape (<i>Vitis vinifera</i>)] h. Asghari et al. (2014) [<i>Pycnocycla spinosa</i>] i. Lavoit et al. (2009a, b) [oak (<i>Quercus ilex</i>)] a. Dudareva et al. (2005) [snapdragon (<i>Antirrhinum majus</i>)] b. Ribeiro et al. (2014) [<i>Lippia origanoides</i> Kunth] c. Ferreira et al. (2018) [sweet wormwood (<i>Artemisia annua</i>)]
Sesquiterpene		Nerolidol ^a	Nerolidol ^b , Artemisinin ^c , Dihydroartemisinic acid ^e , (e)-caryophyllene ^b			

Table 1 continued

Class	Diel	Circadian	Seasonality	Light	Temperature	References
Polyphenols			Gallo-catechin ^b , Gallo-catechin gallate ^b , Epigallocatechin ^b , Epicatechin 3-gallate ^b , Caffeic acid ^{c, d} , Gallic acid ^{c, d} , Ellagic acid ^{d, e} , 1- and 3-O-caffeoylquinic acid ^f	Chlorogenic acid ^a		a. Tegelberg et al. (2004) [silver birch (<i>Betula pendula</i>)] b. Ahmed et al. (2014) [precipitation; tea (<i>Camellia sinensis</i>)] c. Lee et al. (2018) [Chinese cabbage (<i>Brassica rapa</i>)] d. Lombardo et al. (2010) [artichoke (<i>Cynara cardunculus</i>)]
Phenols		Quinic acid ^a			Phloroglucinol ^b	a. Soengas et al. (2018) [Chinese cabbage (<i>B. Rapa</i> spp.) and turnip greens (<i>B. Rapa</i> spp.)] b. Zobayed et al. (2005) [St. John's wort (<i>Hypericum perforatum</i>)] c. Ahmed et al. (2014) [precipitation; tea (<i>Camellia sinensis</i>)] d. Hykkerud et al. (2018) [cloudberry (<i>Rubus chamaemorus</i>)]
Phytosterols					Campesterol	e. Mazur et al. (2014) [red raspberry (<i>Rubus idaeus</i>)] f. Lombardo et al. (2010) [artichoke (<i>Cynara cardunculus</i>)]
Vitamins	Citric acid ^f		Ascorbic acid ^d		Ascorbic acid ^{a, b}	Shamloo et al. (2017) [wheat (<i>Triticum</i> spp.)] a. Cook et al. (2004) [cold response; <i>Arabidopsis thaliana</i>]; b. Ragusa et al. (2017) [broccoli (<i>Brassica oleracea</i>), rocket sprouts (<i>Eruca sativa</i>)] c. Kim et al. (2011) [tobacco (<i>Nicotiana attenuata</i>)]
Hormones	Jasmmonic acid ^b , 12-oxo-phytodienoic acid ^b	Abscisic acid (ABA) ^a , Jasmmonic acids ^a , Salicylic acid ^a				d. Mazur et al. (2014) [red raspberry (<i>Rubus idaeus</i>)] a. Goodspeed et al. (2012) [<i>Arabidopsis thaliana</i>] b. Kim et al. (2011) [tobacco (<i>Nicotiana attenuata</i>)]

Fluctuations in other alkaloids, such as morphine, have been observed in *Papaver somniferum* (Itenov et al. 1999). Morphine levels increased during the day while the water content of latex (classified as a polyterpene) was the highest at night. The authors attributed the fluctuations of in latex water content and morphine to changes in water transport which also fluctuates. Alkaloids in the morphine pathway have also been found to oscillate in hemlock (*Conium maculatum*) (Fairbairn and Suwal 1961). In Hemlock, like poppy, the precursors of morphine, codeine and the stimulant thebaine, decrease at dawn before a morning peak of morphine (Reviewed in Robinson 1974).

Organosulfur compounds (thiols)

Glucosinolates

Glucosinolates are amino acid derived phytochemicals found in the *Brassicaceae* family of plants and have a role in defense against herbivory (Mithöfer and Boland 2012; Singh and Mas 2018). Much of this amino-acid derived phytochemical's economic value is from its link to carcinogen detoxification properties of *Brassica* such as broccoli, cauliflower, cabbage, and Brussel sprouts when hydrolyzed to isothiocyanate upon consumption. These also contribute to taste and flavor profiles. Glucosinolates have been the object of numerous seasonal variation studies with sometimes conflicting findings. Studies mainly focus on the two relatively abundant types of glucosinolates: aliphatic glucosinolates derived from the amino acids alanine, valine, leucine, isoleucine, and methionine; and indoles derived from tryptophan.

Seasonal factors of higher mean temperatures and longer photoperiods were found to correlate with the highest concentrations of glucosinolate across ten *Brassica oleracea* cultivars (Charron et al. 2005). One study reports a sweeter and more desired taste correlated to lower temperatures (Mølmann et al. 2015) while higher glucosinolate levels generally correspond to warmer temperatures. Consumers reportedly selected the sweeter tasting broccoli perhaps at the detriment of the nutraceutical value of the plant. Despite the correlation between generally higher levels of glucosinolate in high temperature, not all glucosinolates were affected similarly within each condition. These results support the findings in

another report showing differential accumulation of glucosinolates in broccoli (*Brassica oleracea*) between spring and winter seasons (Vallejo and Toma 2003).

Terpenoids/essential oils

Isoprenoids iridoids and secoiridoids

Monoterpenes are a class of terpenoids that are known for aromas which is why many of them are used as essential oils. These compounds are controlled by several genes that are circadian regulated (Zeng et al. 2017) and show diel or circadian regulation across many species. For example, diel fluctuations of B-pinene are described in *Artemisia annua* (Lu et al. 2002). As these compounds can be used by the plant in defense against herbivores and as an attractant for pollinators, monoterpenes may fluctuate in anticipation of herbivore or pollinator visitors. A study conducted by Dudareva et al. (2005), found that myrcene and nerolidol, a monoterpene and sesquiterpene, respectively, are controlled by the circadian clock in *Antirrhinum majus*. The components of essential oils in *Pycnocycla spinosa* Decne. ex Boiss were also found to fluctuate throughout the day (Asghari et al. 2014). In this study, citronellyl pentanote levels were the highest in the afternoon, P-cymene and geranyl isovalerate were the highest at dusk, and a-eudesmol peaked in the mid-morning hours. Seasonal variation in monoterpene volatile emissions was observed in Mediterranean oak forests, *Quercus ilex* (Lavoir et al. 2009). In oak, the emission of the volatiles composed of α -pinene, β -pinene, sabinene, myrcene, and limonene showed variation across the season that decreased when water availability was limited.

Sesquiterpenes and sesquiterpene lactones

Temporal regulation of phytochemicals is also important in the development of pharmaceuticals from medicinal plants. The sesquiterpene lactone, artemisinin, a highly effective antimalarial drug, accumulates in low quantities in sweet wormwood (*Artemisia annua*). Costs of artemisinin production and distribution have prevented this drug from reaching many of those who need it. Not only is purified artemisinin expensive, but when used alone, there is concern that it

may lead to resistance. Therefore, the use of artemisinin-based combination therapies (ACT) which lower the risk of resistance is recommended (World Health Organization 2015). ACT treatments have improved outcomes in the treatment of malaria (Rasoanaivo et al. 2011; Elfawal et al. 2012). However, the composition of plant extracts and concentrations of nutraceutical products remain unpredictable. For example, a recent study shows seasonal variation in the accumulation of artemisinin in *A. annua*. The yearly variation and peak seasonal period of accumulation are consistent across three cultivars from Chinese, Brazilian, and Swiss origins when grown in the same field in West Virginia (Ferreira et al. 2018).

Conclusions and perspectives

Disruption of phytochemical timing by climate change

The coordination between plants and the daily and seasonally recurring environmental changes has been optimized through millennia of evolution. However, these environmental patterns are changing. Nights are warming (Peng et al. 2004; Vose et al. 2004; Welch et al. 2010; Kumar et al. 2017), seasonal patterns are shifting (reviewed in Parmesan 2006), and patterns of precipitation are changing (Easterling et al. 2017; Unal et al. 2012; Pal et al. 2013; Keggenhoff et al. 2014; Ganguli and Ganguly 2016; Gitau 2016; Rahimpour et al. 2016; Tye et al. 2016; Mallakpour and Villarini 2017; Roque-Malo and Kumar 2017; González-Zeas et al. 2019). Management and harvesting practices refined to optimize phytochemical production may no longer be suitable to the altered patterns of a changing environment. Yet it is challenging to predict how these changes will impact the phytochemical profile. The changing environmental patterns are complex and may have antagonistic effects on phytochemical profiles, making the combined impact challenging to predict. For example, an increase in CO₂ can lead to an increase in phenolics and a decrease in terpenoids in forest trees in the northern hemisphere while warmer weather leads to an increase in terpenoids and a decrease in phenolics. The combined changes overall are predicted to result in an increase phenolics in foliage and decrease in woody tissue (Holopainen et al. 2018). How these changes in

temperature and CO₂ combine with changes in precipitation patterns on phytochemicals has not yet been explored. Understanding how phytochemicals are affected by daily and seasonal cycles in current conditions and integration of the timing of these events will improve the accuracy of these predictions.

Changes in environmental cycles could also impact the plant's temporal balance with the environment. For example, new climate patterns could allow a herbivore to move into a different temporal niche (Belesky and Malinowski 2016; Porqueddu et al. 2016). If a plant produces defense compounds at a specific time of day or season coincident with the historical highest activity of the herbivores the plant's defenses may not be sufficient to protect the plant in the new conditions. As plants respond and adapt to changing environments, their phytochemical profiles will likely change and can ripple through an entire ecosystem starting with the changes in chemicals that deter herbivores or attract pollinators (Akula and Ravishankar 2011).

Using temporal variation in phytochemicals to improve production

The temporal variation of phytochemicals across time of day and time of year appears to occur in a diverse species of plants. Cognizance of this temporal control can improve efforts to enhance the production of select phytochemicals. When engineering or selecting plants for enhanced phytochemical activity it will be critical to consider that the timing of the target may vary throughout the day and year. During selection, testing candidates for breeding will require monitoring the desired phytochemical at consistent times as harvesting at different times can result in different results (Hasperu  et al. 2011; Pincemail et al. 2012; Ariza et al. 2015). The plant's endogenous clock continues to cycle post-harvest (Goodspeed et al. 2013), and interactions between harvest time and storage length and conditions (Hasperu  et al. 2011) will be important to consider during selection.

Temporal and environmental variation can be used to researchers advantage as a tool to identify regulatory and biosynthetic pathways of desired phytochemicals. Using environmental perturbations to identify regulatory relationships between genes and metabolites has been a successful approach to elucidating the biosynthetic and regulatory components of specialized

metabolites. Genes in glucosinolate metabolism were identified by pairing transcriptional and metabolic responses to sulfur depletion (Hirai et al. 2005, 2006). In a study by Li et al. (2018) that used *Dimocarpus longan* Lour. embryonic calli, to evaluate the impact of photoperiod, light intensity, and light quality on flavonoid content, they mapped the variation across these environmental perturbations to identify regulatory components correlated (or anti-correlated) with the changes in flavonoid content, identifying candidate mechanisms for miRNA as regulators of flavonoid accumulation. This approach can be used to exploit variation that extends across time of day and year to identify biosynthetic components and regulatory pathways for a specific metabolite. The temporal resolution also provides enhanced separation in clustering approaches. Clustering volatiles across time has been used to identify their potential environmental sensitivity (Borges et al. 2013). Knowing the sensitivity of each group can be used to interrogate their relationships, their potential regulation mechanisms, and how each group may respond to changes in climate; making temporal variation a powerful tool for identifying regulatory relationships. Not only is the accuracy of identifying transcriptional regulators through gene networks improved by the addition of temporal information (Madar et al. 2009; Desai et al. 2017; Sanchez-Castillo et al. 2018; Yang et al. 2018), but also can be extended to identifying regulators of metabolite accumulation (Hannah et al. 2010; Pérez-Schindler et al. 2017).

Engineering phytochemical accumulation may also be facilitated by analyzing the daily and seasonal flux in the phytochemical profile. For example, efforts to engineer plants to enhance artemisinin production or other compounds for pharmaceutical or industrial use requires increasing the concentration, storage, deliverability, stability, purity, and performance of the desired phytochemical (Pulice et al. 2016). Each of these steps can be affected by environmental factors, and production of phytochemicals can be improved by considering environmental stresses (reviewed in Rai et al. 2011; Naeem et al. 2017; Aftab et al. 2018). As plants tightly control the timing of their metabolism and stress responses, working within the framework of this temporal regulation will aid efforts to enhance production. Strategies to enhance production through altering environmental stimuli (Fujiuchi et al. 2016; Huang et al. 2016) will likely benefit from considering

the native rhythm of environmental stresses and the endogenous plant response to maximize the effectiveness of the treatments. Designing molecular and biochemical strategies that integrate the temporal variation in primary and specialized metabolism may improve the success in optimizing phytochemical production.

For some medicinal products, whole-plant extracts have added benefits over single molecule products (Adwan and Mhanna 2008; Deharo and Ginsburg 2011; Herranz-López et al. 2018). Inconsistencies in whole-extract profiles can impact their efficacy and acceptance as a viable alternative to single products. Considering the temporal variation in both the primary bioactive product and synergistic molecules may reduce variation between producers, which could lead to improved acceptance. To ensure the efficacy of the product, producers will need to understand the best time to grow and harvest the crop to optimize the concentration of the target metabolite while also quantifying active metabolites in the overall profile with antagonistic or synergistic effects.

Conclusions

In a review by Robinson (1974) there is a quote from the works of Theophrastus in the 4th century BC, “some roots should be gathered at night other by day, and some before the sun strikes on them.” Over 2000 years later, molecular and biochemical evidence is mounting in support of this advice; that time is an important consideration in the study of phytochemicals. Understanding the impact of time on phytochemical composition can help to optimize phytochemical production, enhance the quality of our food, and efficiently meet the increasing demand for phytochemicals in the background of a rapidly changing climate.

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