Dietary Chronobiotics: Polyphenols and Plant Melatonin

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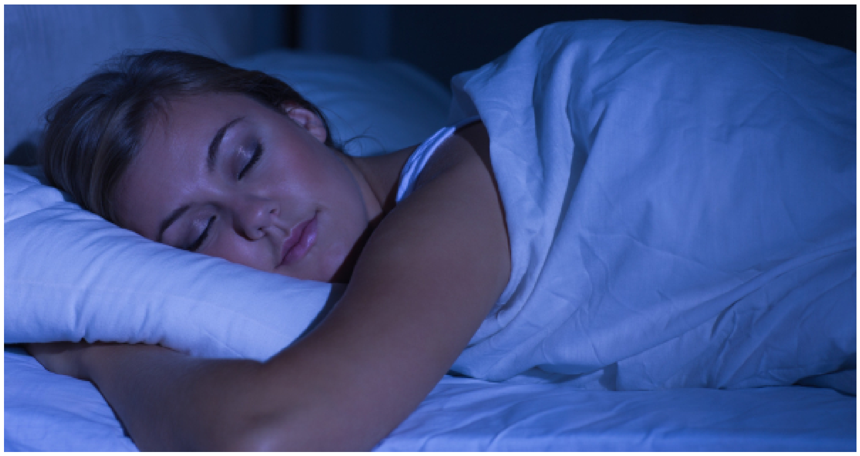
Written By: Deanna Minich, PhD (/gmi-blogs/deannaminich)



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Everyone is affected by environmental fluctuations, whether yearly with the changing seasons or daily with cycles of lightness and darkness. Monthly changes are seen with the menstrual cycle and lunar phases, and transition phases like menopause or puberty occur once but are mostly consistent across all humans. Humans adapt to these rhythms with internal clocks that drive the lifecycle, health, and day-to-day life and behaviors; **chronobiology (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785655/)** refers to these biological rhythms.

The Circadian Rhythm and the Dangers of Artificial Light at Night (ALAN)

The circadian rhythm is a 24-hour sleep-wake cycle. Circadian clocks generate it, and the **suprachiasmatic nucleus (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9963929/)** (SCN) in the hypothalamus is the primary circadian clock. Light exposure during the day **sets (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9963929/)** circadian clocks and synchronizes physiology to exogenous or environmental cues. However, because light is the most **potent (https://www.cell.com/current-biology/fulltext/S0960-9822(06)02609-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0960982206026091%3Fshowall%3Dtrue)** cue or "zeitgeber," too much light exposure at night can **interfere (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9963929/)** with and dysregulate the circadian rhythm, ultimately impacting physiology and behavior, and potentially increasing the risk of disease. For example, **exposure (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5897701/)** to artificial light at night (ALAN) can cause changes in thyroid hormone, glucocorticoids (e.g., cortisol), and gonadotropic hormones (i.e., luteinizing hormone and follicle-stimulating hormone). ALAN from **light pollution (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7764771/)** is associated with risk for cancer as it can increase tumorigenesis. Finally, ALAN is **implicated (https://www.mdpi.com/2673-6004/3/1/3)** in impaired brain function and may contribute to learning and memory deficits and mood changes like depression.

Of note, those with light-colored eyes may be more **susceptible (https://pubmed.ncbi.nlm.nih.gov/17332164/)** to the suppressive effects of light at night on **melatonin** (/substance/melatonin), a hormone involved in the sleep-wake cycle, compared to those with dark eyes. However, light-eye individuals may be less **prone (https://pubmed.ncbi.nlm.nih.gov/11816051/)** to Seasonal Affective Disorder (SAD). On the other hand, bright light in the morning and during the day can support the circadian rhythm by **increasing (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10056135/)** melatonin levels at night.

Melatonin

Chronobiotics (https://pubmed.ncbi.nlm.nih.gov/16596316/) are substances that can set the circadian rhythm. A well-known chronobiotic is melatonin, a hormone produced and secreted during darkness that promotes sleep. Given its role in the circadian rhythm, melatonin has **diurnal (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1855314/)** variations and begins to rise 2-3 hours before sleep, peaks between 2 am to 4 am, and declines with daylight. Melatonin also has its own rhythm throughout the lifecycle, **peaks (https://pubmed.ncbi.nlm.nih.gov/17408483/)** in early childhood, declines through adulthood, and is nearly negligible in older adults.

Melatonin is **produced (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8836571/)** by the pineal gland, among other organs, including the gastrointestinal tract, brain, adrenal gland, heart, thymus, placenta, reproductive system, kidney, and immune cells. Besides its effect on the sleep-wake cycle, **melatonin (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8836571/)** regulates body temperature and hormone synthesis, activates the immune system, protects the skin from UV radiation, regulates skin pigmentation, and slows aging. It also has cardioprotective, antioxidant, and cytoprotective effects. When melatonin concentrations are disrupted, there may be **changes (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9963929/)** in hormone rhythms of the thyroid, adrenals, and reproductive system. Low melatonin is also **associated (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3354573/)** with various conditions, including Alzheimer's disease, insulin resistance, type 2 diabetes, fibromyalgia, certain types of cancer, and migraines.

Melatonin may be neuroprotective and support several aspects of cognitive health. One **study (https://pubmed.ncbi.nlm.nih.gov/36634691/)** found that melatonin treatment involving 3 mg of melatonin per night for three months restored circadian rhythm and increased brain-derived neurotrophic factor (BDNF) in obese children. However, another **study (https://pubmed.ncbi.nlm.nih.gov/36049659/)** found that, while melatonin did not increase BDNF, it did improve depression. Melatonin may also **protect (https://pubmed.ncbi.nlm.nih.gov/36871878/)** against arsenic-induced neurotoxicity, and cell and animal studies show that it **decreases (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6932927/)** the permeability of the blood-brain barrier. Finally, sleep may facilitate the removal of toxins in the brain via **glymphatic fluid (https://pubmed.ncbi.nlm.nih.gov/24136970/)**, an area where cerebral spinal and interstitial fluid come together by the cerebral blood vessels. Melatonin **secreted (https://pubmed.ncbi.nlm.nih.gov/36917314/)** into the cerebral spinal fluid potentially helps to flush harmful molecules like amyloid-β peptide - a hallmark of Alzheimer's disease - from the brain. Notably, melatonin promotes sleep, and waste clearance from the central nervous system is **highest (https://pubmed.ncbi.nlm.nih.gov/36917314/)** during slow-wave sleep.

Polyphenols

Polyphenols (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893786/) are the largest category of phytochemicals and include compounds like catechins, ellagic acid, resveratrol, quercetin, and isoflavones. Plant foods, including grapes, berries, cocoa, coffee, tea, herbs, and spices, are rich in polyphenols and have antioxidant and anti-inflammatory effects. The brain is **sensitive (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10451187/)** to oxidative damage, and by lowering oxidative stress, **polyphenols** (/substance/polyphenols) can protect against neurological conditions. The effects of polyphenols extend to autophagy and detoxification, epigenetic modification, the microbiome, and metabolic effects, all of which lead back to the brain.

The brain-promoting activities of polyphenols are wide-ranging. In animal models of **Alzheimer's disease** (/disease/alzheimers-disease), it is shown that **epigallocatechin gallate (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10048542/)** (EGCG) may prevent and treat Alzheimer's disease; **quercetin (https://pubmed.ncbi.nlm.nih.gov/30914316/)** reduces deposition of amyloid beta-protein in the hippocampus and amygdala; and **curcumin (https://pubmed.ncbi.nlm.nih.gov/31590042/)** improves cognitive performance. **Urolithins (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9858309/)** are metabolites of ellagitannins produced by the gut microbiota that are shown to stabilize the intestinal barrier and blood-brain barrier. A 12-month randomized controlled **trial (https://pubmed.ncbi.nlm.nih.gov/31711104/)** found that pomegranate juice, which is rich in polyphenols like ellagitannins, helped maintain visual memory performance in individuals (ages 50-75) who were considered to have cognition consistent with normal aging or mild cognitive impairment. In the study, participants consumed either 8 oz of pomegranate juice per day or a placebo drink with the same flavor, color, sugar, and acidity level of pomegranate juice but did not contain pomegranate polyphenols. Additionally, polyphenols may **improve (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9916817/)** symptoms of depression by reducing inflammation and oxidative stress, modulating neurotransmitter systems involving neurotransmitters like GABA, serotonin, and dopamine, modulating the HPA axis; and increasing cerebral blood flow.

Some polyphenols may **affect (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7417799/)** clock genes and regulate the circadian rhythm. For example, EGCG, the primary catechin in green tea, may **regulate (https://pubmed.ncbi.nlm.nih.gov/28412321/)** the expression of circadian clock genes and improve circadian function affected by a Western diet. This effect may **improve (https://pubmed.ncbi.nlm.nih.gov/28412321/)** obesity-related parameters, such as glucose homeostasis and body weight. Some studies imply that another polyphenol, **resveratrol (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10289927/)**, can impact the circadian rhythm by upregulating Sirtuin 1 (SIRT1), a circadian regulator. Interestingly, resveratrol pharmacokinetics exhibits **circadian (https://pubmed.ncbi.nlm.nih.gov/19194969/)** variation and has higher bioavailability in the morning**.** One **study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7417799/)** investigated the effects of cacao polyphenols on the expression of circadian clock genes in mice using cacao liquor procyanidin, an extract abundant in catechin, epicatechin, and procyanidins. Results showed that the cacao extract regulated the expression of circadian clock genes by activating GLP-1 and AMP-kinase pathways.

Circannual Rhythms: Chronobiology Throughout the Year

Fluctuations in the environment throughout the year are primarily marked by the changing seasons. Fluctuating environmental factors, such as melatonin, vitamin D, and UV radiation, may profoundly impact health, including the **activity (https://www.sciencedirect.com/science/article/abs/pii/S089684111730313X?via%3Dihub)** of autoimmune disorders. Changing levels of melatonin and vitamin D may cause circadian rhythm disruption, which can lead to an **increase (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10419593/)** in pro-inflammatory cytokines and contribute to autoimmune disease.

One published **article (https://pubmed.ncbi.nlm.nih.gov/28624334/)** summarizes the relationship between seasons and autoimmune diseases:

- **Multiple Sclerosis (MS)** is an autoimmune condition involving the myelin of the central nervous system. It has **higher (https://pubmed.ncbi.nlm.nih.gov/28624334/)** onset rates in the spring when vitamin D and melatonin are both low. **March and April (https://pubmed.ncbi.nlm.nih.gov/36171477/)** show higher relapses in MS patients compared to other months. Several studies have found that spring **birth months (https://pubmed.ncbi.nlm.nih.gov/28624334/)** are associated with a higher susceptibility to MS than winter birth months. The connection between birth month and MS is more robust in individuals with increased **genetic (https://pubmed.ncbi.nlm.nih.gov/28624334/)** risk, and it may be related to low maternal levels of vitamin

D during the prenatal and perinatal periods, increasing the risk of MS development in the spring. Melatonin may have an **immunosuppressive (https://pubmed.ncbi.nlm.nih.gov/28624334/)** role, and low levels in the spring may increase the relapse rate of MS.

- **Systemic Lupus Erythrematosis (SLE)** exhibits **seasonal (https://pubmed.ncbi.nlm.nih.gov/28624334/)** patterns related to UV exposure, the occurrence of infections, and vitamin D levels, a nutrient inversely associated with disease activity. During winter months, there is a **higher (https://pubmed.ncbi.nlm.nih.gov/28624334/)** rate of non-cutaneous and nephritic flares of lupus. Additionally, infections like Epstein-Barr virus (EBV), a human herpes virus, are **implicated (https://pubmed.ncbi.nlm.nih.gov/28624334/)** in the development of SLE and are more prevalent during the winter, though the connection needs more research. On the other hand, UV radiation in the summer **aggravates (https://pubmed.ncbi.nlm.nih.gov/28624334/)** cutaneous lupus.
- **Irritable Bowel Disease (IBD)** consists of Crohn's disease (CD) and ulcerative colitis (UC). Rates of ulcerative colitis diagnosis have been shown to **increase (https://pubmed.ncbi.nlm.nih.gov/28624334/)** in April, and April birth months have a higher risk of UC development compared to October birth months. The trend may be **connected (https://pubmed.ncbi.nlm.nih.gov/28624334/)** to UV exposure and vitamin D levels during the third trimester.

The bioavailability of polyphenols can be impacted by time of year and growing method. Thus, they have their own seasonal variations. An animal **study (https://pubmed.ncbi.nlm.nih.gov/31525717/)** using grapes found that when rats were exposed to light conditions (short photoperiod) simulating winter light exposure, their metabolite concentrations from the grapes were at their highest compared to conditions simulating spring, summer, and autumn light exposure. In other words, these grape polyphenols have enhanced metabolism in the simulated winter condition compared with the other light simulations. The study also found that organic grapes had better polyphenol bioavailability than conventionally-grown grapes, as shown by higher serum concentrations of metabolites. Another animal **study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7058598/)** using oranges from the southern and northern hemispheres showed that orange consumption out of season led to fat tissue accumulation. The study analyzed approximately 39 phytochemicals, and the two oranges differed in 24 of them. The xenohormesis **theory (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7058598/)** explains that humans and other heterotrophs respond to bioactive compounds, such as polyphenols, in food to facilitate adaptation to the environment or changing seasons, which may impact fat storage. The synthesis of these polyphenols are modulated by **environmental factors (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893786/)**, including water, light, temperature, and soil salt, thus connecting them to the changing seasons. This concept is also seen with sweet cherries, typically consumed in the spring and summer when days are long. In an animal **study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6115965/)**, the metabolism of adipose tissue differed depending on the photoperiod, or whether or not the fruit was consumed in or out of season, simulated by hours of light exposure. When the cherries were consumed out of season, the animal was more prone to fat accumulation.

Supplementation and Phytomelatonin

Melatonin has far-reaching impacts on health, and clinically, **melatonin (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)** has the potential to be used for circadian rhythm support, cognitive conditions, migraines and headaches, tinnitus, metabolic syndrome, fertility, irritable bowel syndrome, autoimmune disorders such as Hashimoto's thyroiditis, coronavirus disease, osteopenia, and more. Supplemental melatonin is available over-the-counter, and its use among **US adults (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8808329/)** is on the rise. While melatonin is generally regarded as safe, the actual melatonin content of supplements may be between -83% to up to **478% (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5263083/)** higher than advertised and may contain **serotonin (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5263083/)**, which is considered a controlled substance used to treat neurological disorders. Because supplements come in a range of doses from 0.3 mg to 200 mg, individuals could be consuming very high amounts of melatonin. The pineal gland produces about **0.3 - 0.9 mg (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)** of melatonin per day. Most melatonin supplements are synthetically **produced (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)** through a multi-chemical step process involving products like acetone, ethanol, and cold petroleum ether, and the facilities that make them create significant pollution. However, nearly all melatonin, whether synthetic, "plant-based," or "natural," **involves (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)** industrial processing that may use toxic substances. Contrary to popular belief, melatonin supplementation does not impact **endogenous (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3150476/)** production. However, **high (https://ep.bmj.com/content/90/3/ep74)** doses of melatonin over long periods could potentially reduce the sensitivity of receptor sites, creating a need for higher quantities.

Phytomelatonin is a bioidentical melatonin produced by plants. Compared to synthetic melatonin, phytomelatonin has **higher (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8512846/)** anti-inflammatory and free radical scavenging activity. **Foods (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)** such as cherries, almonds, walnuts, flaxseeds, sunflower seeds, oats, black pepper, and many more contain varying amounts of melatonin. However, the melatonin content of plants is inconsistent and depends on several factors, **including (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5409706/)** cultivars and growing conditions. Because tryptophan - an essential amino acid - is **converted (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8761603/)** to serotonin and then melatonin, tryptophan intake should be included when considering food sources of melatonin. However, not all individuals efficiently convert tryptophan to melatonin due to gene **variants (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)** related to the N-acetylserotonin methyltransferase (ASMT) enzyme.

Besides consuming food sources of tryptophan, dietary and lifestyle support for melatonin production **includes (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9571539/)**:

- Receiving adequate darkness at night.
- Reducing artificial blue light at night includes limiting cell phone and computer use, avoiding LED lightbulbs, and using blue-light-blocking glasses if using screens.

- Eating adequate protein and an anti-inflammatory diet.
- Eating food sources with blue-light protective nutrients, such as **lutein and zeaxanthin (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5331551/)** (e.g., kale, spinach, parsley, peas, lettuce, squash, and pumpkin).

If you have questions about which foods or supplements can best support your health, talk to your doctor, nutritionist, dietician, or another healthcare team member for personal options based on your circumstances.

 (/gmi-blogs/deannaminich)

Dr. Deanna Minich (http://deannaminich.com/) is a wellness and lifestyle medicine expert who integrates ancient healing traditions with modern science. Her unique "whole self" approach to nutrition looks at physiology, psychology, eating, and living within what she calls the "7 Systems of Health." Founder of **Food & Spirit** (http://www.foodandspirit.com), she also leads online detox programs. Her latest book is ***Whole Detox: A 21-Day Personalized Program to Break Through Barriers in Every Area of Your Life*** (HarperCollins, 2016)

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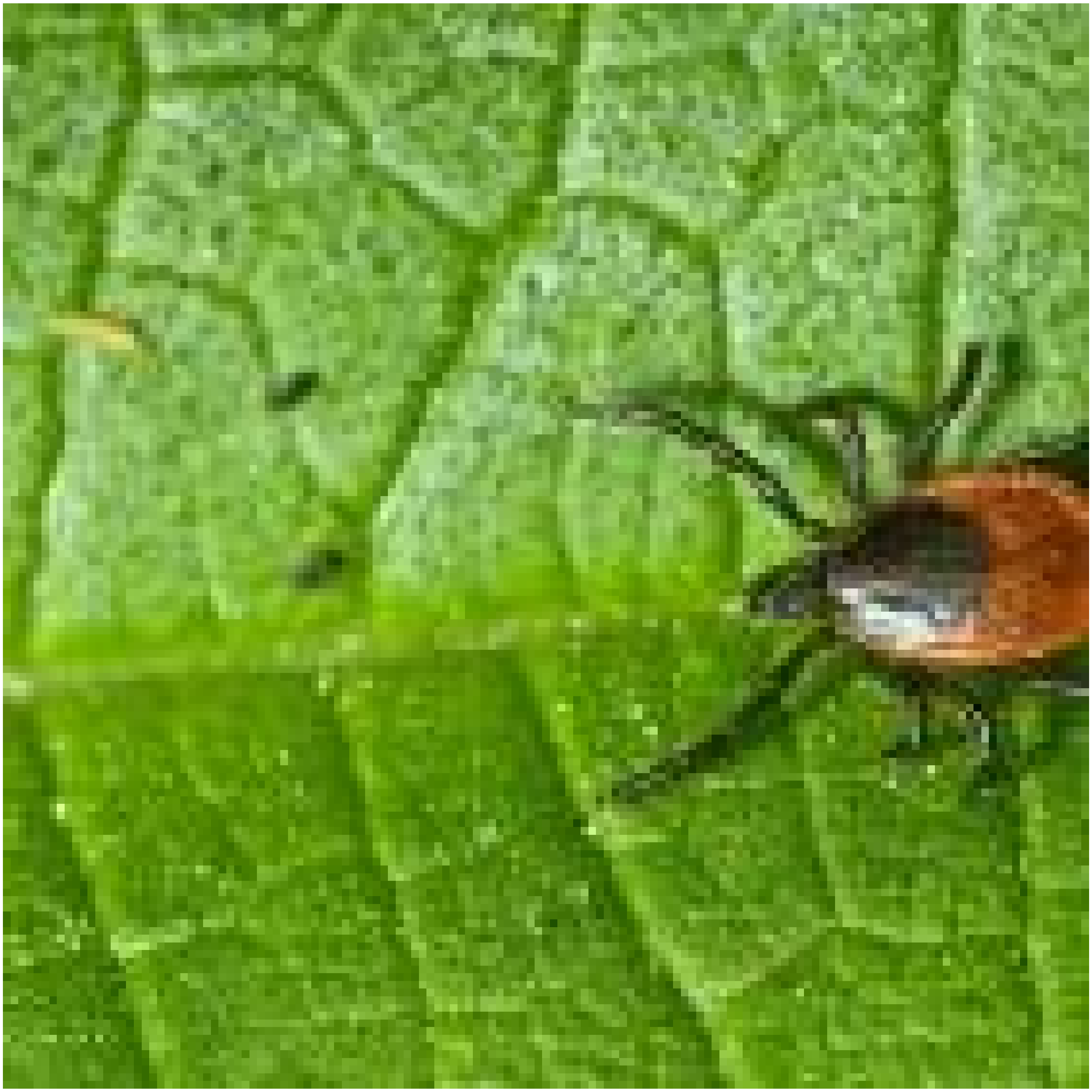
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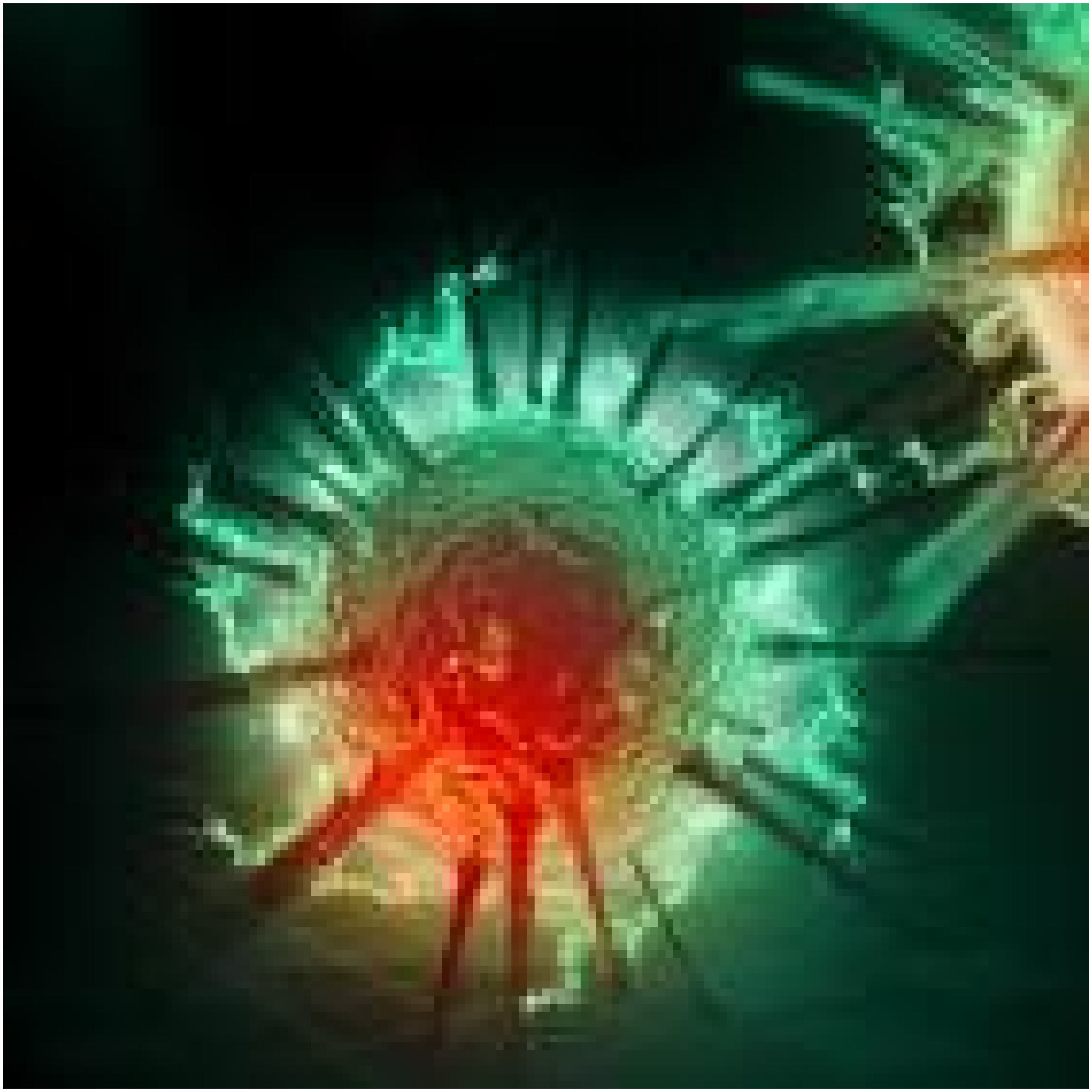

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