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# Blueberries and raspberries as endocrine modulators: Mechanisms, clinical evidence, and translational guidance

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**ABSTRACT**

Endocrine pathways are increasingly recognized as important targets for preventive and adjunctive care. Blueberries (Vaccinium spp.) and raspberries (Rubus spp.) are particularly rich in anthocyanins, ellagitannins, and related flavonoids with hormone-modulating properties. Recent evidence from mechanistic and clinical studies, particularly in 2023–2024, suggests that berry-derived bioactives impact estrogen receptors, insulin signaling, and the hypothalamic–pituitary–adrenal (HPA) axis. Yet issues of bioavailability, microbiome conversion, and dosing remain insufficiently integrated.

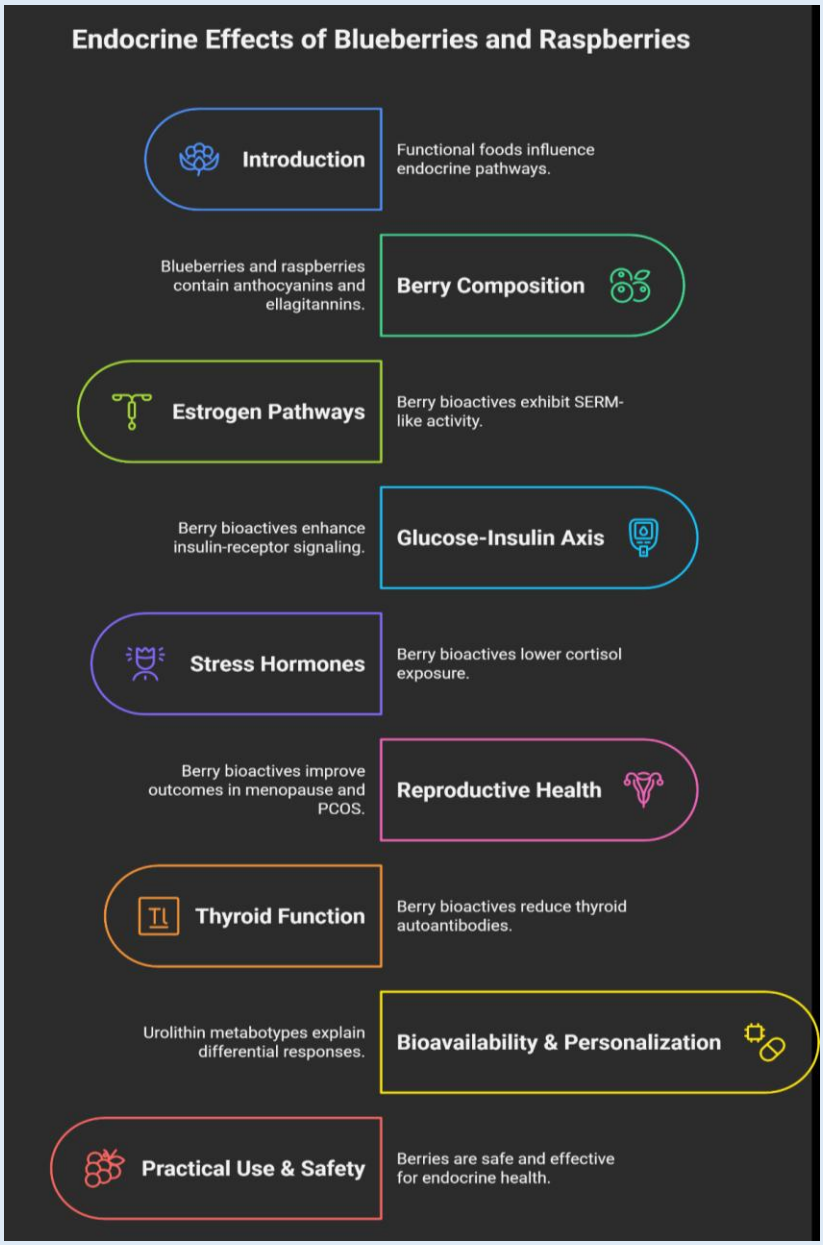
Key findings highlight selective estrogen receptor modulator–like activity that improves estrogen metabolism and menopausal health; enhanced insulin sensitivity via AMPK activation, insulin receptor signaling, and α-amylase/α-glucosidase inhibition; and HPA axis modulation with reduced cortisol exposure and improved circadian rhythms. Clinical trials in peri- and postmenopausal women report better sleep, mood, and hot-flash outcomes, while pilot studies in polycystic ovary syndrome (PCOS) suggest improved insulin sensitivity and lower androgen levels. Preliminary data also indicate antioxidative and immune-modulatory effects on thyroid function.

Whole berries (≈150–200 g/day) or standardized freeze-dried equivalents consistently deliver endocrine-relevant benefits with excellent tolerability. Although plasma levels of parent anthocyanins are low, microbiome-derived metabolites such as urolithins and inter-individual variability in metabolism likely shape clinical responses.

Blueberries and raspberries act as multi-target endocrine modulators through receptor, enzyme, neuroendocrine, and microbiome-mediated mechanisms. Their routine dietary inclusion represents a practical, safe strategy to support hormonal balance across life stages. Large-scale trials remain essential to define effective dosing, compare whole fruits versus extracts, and explore personalized nutrition approaches.

**Novelty:** This study is among the first to integrate mechanistic, clinical, and translational evidence on blueberries and raspberries as endocrine modulators. Unlike prior research focusing on single pathways, we highlight their combined effects on estrogen receptors, insulin signaling, and the HPA axis, while also considering microbiome-derived metabolites such as urolithins. By synthesizing recent 2023–2024 findings, this work reframes these berries as clinically relevant functional foods with the potential to support menopausal health, PCOS, and broader hormonal balance.

**Keywords:** flavonoids; anthocyanins; ellagitannins; endocrine function; blueberries; raspberries; phytochemicals; insulin sensitivity; stress hormones




**Graphical Abstract:** Blueberries and raspberries as endocrine modulators: mechanisms, clinical evidence, and translational guidance.

## INTRODUCTION

Diet–hormone interactions have emerged as a central theme in nutrition science, with specific bioactives demonstrating the capacity to affect endocrine pathways. Within this landscape, blueberries and raspberries have gained prominence owing to high concentrations of flavonoids and other phytochemicals with putative hormone-modulating properties. Maintaining hormone homeostasis is essential for metabolic regulation, reproduction, stress adaptation, and overall health; dysregulation is linked to diabetes, cardiovascular disease, reproductive disorders, and metabolic syndrome. Diet-derived modulators thus present opportunities for prevention and adjunctive therapy.

Blueberries (Vaccinium angustifolium, V. corymbosum) and raspberries (Rubus idaeus, R. occidentalis) provide anthocyanins, proanthocyanidins, flavonols, flavanols, ellagitannins, and phenolic acids [1–4]. These constituents can act at multiple levels—biosynthesis, metabolism, transport, receptor engagement, and downstream signaling—to influence endocrine outcomes [5–8]. Clarifying these mechanisms supports evidence-based intake recommendations for hormone health [9–10]. Here we review current evidence, prioritizing recent mechanistic insights and clinical results that inform translational use across populations and conditions. We also emphasize pragmatic considerations—dose, matrix, timing, and inter-individual variability—that matter when translating findings to practice.

The broader public-health rationale is two-fold. First, endocrine-related conditions impose substantial global morbidity and cost; scalable, food-based strategies could complement standard care without adding medication burden. Second, berries are widely available, palatable, and culturally adaptable, improving the odds of real-world adherence relative to nutraceuticals or restrictive diets. Accordingly, we frame evidence not only around biological plausibility and efficacy but also feasibility—what amounts, forms, and frequencies are realistic for long-term patterns.

Beyond broad links between diet and endocrine control, a finer-grained picture is emerging in which berry bioactives engage specific nodes of hormone networks rather than acting as generic antioxidants [1,5,9]. For example, catechol-estrogen homeostasis is influenced by anthocyanin-driven shifts in cytochrome P450 activity and conjugation capacity, potentially redirecting metabolism toward less estrogenic and less genotoxic metabolites [1,9-10]. Parallel effects on insulin signaling, HPA-axis tone, and reproductive hormone dynamics suggest that these foods operate as multi-target modulators whose net impact depends on life stage, sex, genetics, and the gut microbiome [2,6-7,10]. Framing blueberries (Vaccinium spp.) and raspberries (Rubus spp.) as precision nutrition tools rather than one-size-fits-all “superfoods” helps reconcile inter-individual variability observed in trials and sets the stage for mechanism-grounded clinical translation [2,4,9-10].

A practical implication is that matrix and dosing matter. Whole fruit, freeze-dried powders, and standardized extracts deliver different anthocyanin profiles and release kinetics, which interact with circadian rhythms, meal composition, and medication timing to shape endocrine outputs [3-4,9]. The present review integrates mechanistic, clinical, and population data to define when and how these berries can be deployed to support endocrine health, while flagging where evidence is preliminary and where rigorous trials are still needed [1-2,9-10].

## METHODS

We conducted an electronic literature review on blueberries and raspberries as endocrine modulators by searching PubMed and the Functional Food Center’s journal platform (Food Science Publisher; FFHDJ.com) for studies published January 1, 2019–August 31, 2025. Search terms combined concepts for berries and their

bioactives (e.g., blueberries, raspberries, anthocyanins, ellagitannins, flavonoids) with endocrine outcomes and mechanisms (e.g., endocrine function, estrogen metabolism, insulin sensitivity, stress hormones/HPA axis). Records were de-duplicated; titles/abstracts were screened, and full texts were assessed for eligibility. We included peer-reviewed original research and reviews that provided evidence on endocrine mechanisms, clinical outcomes, or translational guidance; non-English articles were excluded. (Illustrative Boolean string: (blueberries OR raspberries) AND (anthocyanins OR ellagitannins OR flavonoids) AND ("endocrine function" OR "estrogen metabolism" OR "insulin sensitivity" OR "stress hormones").)

## Bioactive Compounds in Blueberries and Raspberries

**Flavonoid Profile and Content:** Blueberries and raspberries are distinguished by substantial flavonoid content, albeit with variation by cultivar, agronomy, ripeness, processing, and storage. Dominant classes include anthocyanins, flavonols (e.g., quercetin, myricetin), flavanols (catechin/epicatechin), and proanthocyanidins, each with distinct bioactivities relevant to endocrine outcomes. Anthocyanins are the most abundant class and underpin both coloration and many biological effects [11–12]. In blueberries, prevalent anthocyanins include delphinidin-3-glucoside, cyanidin-3-glucoside, petunidin-3-glucoside, peonidin-3-glucoside, and malvidin-3-glucoside [3,13–14], which exhibit antioxidant effects and interact with hormone signaling pathways [15–17].

Across compositional surveys, total anthocyanin content in highbush blueberries typically spans low double-digits to several hundred milligrams per 100 g fresh weight, with wild/lowbush cultivars trending higher; raspberry totals are generally lower but accompanied by meaningful levels of cyanidin derivatives and unique glycosides [3,11,18-19]. Processing modulates content and bioaccessibility: freeze-drying and gentle dehydration retain anthocyanins better than thermal processing, while matrix components (pectin, organic acids) can stabilize pigments during digestion [4,19–20]. Such variability partly explains heterogeneous outcomes across trials and supports the need for standardized preparations when comparing studies [19]. Analytical choices also matter: HPLC-DAD/LC-MS profiling yields precise anthocyanin fingerprints, whereas colorimetric assays (e.g., total phenolics by Folin–Ciocalteu) can overestimate due to non-phenolic reducers; harmonized reporting enhances cross-study interpretation [19].

Bioactivity is not dictated solely by parent anthocyanins. Phase I/II transformation and microbial catabolism yield smaller phenolics and conjugates with distinct kinetics and receptor affinities [4,12–14]. Proanthocyanidins, abundant in blueberries, comprise flavan-3-ol oligomers with reported interactions at steroid receptors and metabolizing enzymes; chain length and galloylation patterns may influence estrogen-related endpoints and tissue distribution [18]. Co-pigmentation with flavonols and phenolic acids can stabilize anthocyanins through π–π stacking, enhancing gastric stability and potentially modifying absorption kinetics [4,14,19].

Chemical diversity within anthocyanins extends beyond aglycones to glycosylation patterns (e.g., 3-glucosides, rutinosides) and acylation, factors that alter stability, transporter recognition, and downstream metabolite profiles relevant to hormone signaling [3,11,14]. Cultivar, ripeness, storage, and processing each shift these patterns; for instance, freeze-drying tends to preserve delphinidin and malvidin conjugates, whereas thermal processing can favor smaller phenolic acids formed from anthocyanin cleavage—metabolites increasingly recognized as active effectors at endocrine targets [4,12,14]. Co-occurring flavonols and proanthocyanidins may synergize through complementary receptor interactions or by modulating

enzymes that determine anthocyanin residence time in target tissues [3,11,18]. Such compositional nuance helps explain why apparently similar doses yield heterogeneous physiological readouts across studies [1,3,12,14]. See Table 1 for a concise overview of major bioactives, endocrine targets, and actions

**Table 1.** Bioactive classes in blueberries and raspberries with endocrine-relevant targets and actions.

| Compound Class | Key Molecules (Examples) | Primary Endocrine Targets | Representative Actions | Notes On Variability |
|---|---|---|---|---|
| **Anthocyanins** | Delphinidin-, cyanidin-, malvidin-3-glucosides | ERα/ERβ; insulin signaling; 11β-HSD1 [3,11,14–17,19] | ↑AMPK; ↑UGT/SULT; ↓CYP1B1 [3,11,14–17,19] | Cultivar; glycoside pattern; processing [19] |
| **Flavonols** | Quercetin; myricetin | ERβ; Nrf2/antioxidant [3,14] | Redox support; co-pigmentation [3,14] | Co-occurs with anthocyanins [3,14] |
| **Flavanols** | Catechin; epicatechin | Insulin signaling; endothelial NO [11,16] | ↑GLUT4; ↓NF-κB [11,16] | Degree of polymerization [11,16] |
| **Proanthocyanidins** | Oligomeric flavan-3-ols | ER co-regulators; steroid enzymes [18] | Co-activator modulation [18] | Chain length; galloylation [18] |
| **Ellagitannins / ellagic acid** | Sanguiin H-6; lambertianin C | ERα/ERβ (SERM-like); steroidogenesis [5,7,20–28] | Urolithin formation; tissue selectivity [5,7,20–28] | Microbiome metabotypes (A/B/0) [21–25] |
| **Phenolic acids** | Chlorogenic; caffeic; ferulic | Inflammation; bile acids; COMT [4,12,14] | Anti-inflammatory; transporter effects [4,12,14] | Matrix & meal context [4,12,14] |
| **Soluble fiber** | Pectin | GLP-1; FXR/TGR5; enterohepatic [9,10,30] | SCFAs; improved insulin dynamics [9,10,30] | Titrate for GI tolerance [30] |

**Ellagitannins and Ellagic Acid:** Raspberries are exceptional sources of ellagitannins, particularly in seeds, which appear central to hormone-modulating effects [5,20,21–22]. During digestion, ellagitannins release ellagic acid and are further transformed by the gut microbiota to urolithins with potent bioactivities [7,23–25]. Recent work characterizes ellagitannins as selective estrogen-receptor modulators (SERMs) with tissue-dependent agonist/antagonist actions [5,7,22,26], supporting their value across life-stage contexts [20,27–28]. Conversion to urolithins is highly microbiome-dependent, producing inter-individual variability in response and underscoring the need for personalized guidance [23–25]. Three recurring metabotypes are described: A (urolithin A producers), B (urolithin B/isourolithin producers), and “0” (non-producers), with emerging associations to differential endocrine responses and inflammatory tone [23–25].

A key advance has been the identification of urolithin metabotypes—inter-individual patterns (A, B, or 0) of converting ellagitannins/ellagic acid into urolithins—driven largely by gut microbial composition [21,23–25]. Because urolithins differ in estrogen receptor affinity and anti-inflammatory potency, metabotype status likely conditions clinical responsiveness in hormone-linked outcomes [21,23–25]. Seeds of raspberries are particularly rich in high-molecular-weight ellagitannins that release ellagic acid gradually during digestion, potentially sustaining urolithin production and extending exposure windows for receptor-level effects [20,2122]. Early mechanistic work suggests selective estrogen receptor modulation alongside interference with steroidogenic enzymes, offering a SERM-like profile that is tissue-context dependent [5,7,22].

**Additional Bioactive Constituents:** Beyond flavonoids and ellagitannins, phenolic acids (e.g., chlorogenic, caffeic,

ferulic) exert anti-inflammatory effects and interact with hormone signaling cascades. Soluble fibers—particularly pectin—shape the endocrine milieu indirectly via microbiota fermentation to short-chain fatty acids (SCFAs), bile-acid signaling through FXR/TGR5, and modulation of post-prandial glucose/insulin dynamics. Micronutrients (vitamin C, vitamin K, manganese, folate) serve as cofactors in hormone synthesis and metabolism, acting synergistically with polyphenols to support endocrine function. Interactions with transport proteins (e.g., OATPs) and binding to hormone-carrier proteins may further influence tissue targeting and bioavailability [16,25,29].

Soluble fiber (notably pectin) and associated polyphenol–fiber complexes shape bile acid pools and microbial ecology in ways that feedback on GLP-1 signaling, insulin dynamics, and estrogen recirculation via enterohepatic pathways [9,30]. Micronutrients—including vitamin C as a cofactor for catecholamine biosynthesis and manganese for antioxidant enzymes—may amplify or stabilize polyphenol effects within endocrine tissues [10]. While individually modest, these matrix-level contributions likely compound the hormonal benefits observed with whole-berry intake compared to isolated compounds [9-10].

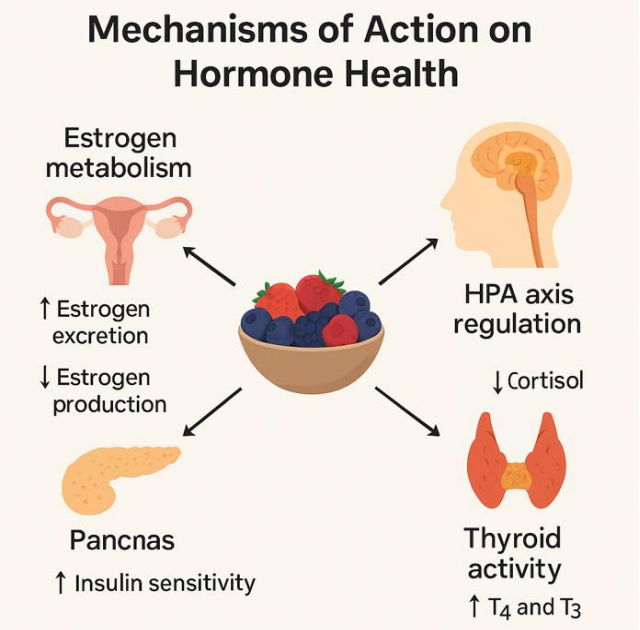



**Figure 1:** Proposed mechanisms by which berry bioactives modulate endocrine function, including estrogen metabolism, insulin signaling, HPA axis regulation, and thyroid activity.

## Mechanisms of Action on Hormone Health

**Estrogen Metabolism and Signaling**: Berry bioactives influence estrogen pathways via receptor engagement, metabolic enzyme modulation, and transport/clearance. Anthocyanins and related flavonoids display weak estrogenic/anti-estrogenic activity at ERα/ERβ, consistent with SERM-like effects that can benefit both low- and high-estrogen states. Modulation of Phase I enzymes (CYP1A1, CYP1A2, CYP1B1) shifts metabolite profiles toward less potent forms, while induction of Phase II conjugation (UGTs, SULTs) enhances clearance and may mitigate estrogen dominance.

At the catechol-estrogen node, favoring 2-hydroxylation over 16α-hydroxylation is considered beneficial; downstream methylation by catechol-O-methyltransferase (COMT) yields methoxyestrogens with reduced reactivity. Several berry constituents upregulate protective routes and suppress quinone formation that can lead to DNA adducts, aligning with improvements in 2-hydroxyestrone:16α-

hydroxyestrone ratios observed clinically [4,31]. Proanthocyanidins may also alter estrogen-receptor co-activator recruitment, and ellagitannin-derived urolithins show tissue-selective partial agonism/antagonism at ER subtypes [5,7,22]. Hepatic transporter interactions and enterohepatic cycling further modulate systemic exposure and excretion [14,29]. In parallel, redox-sensitive transcription factors (e.g., Nrf2) are activated by anthocyanins, elevating detoxification enzymes that intersect with estrogen metabolism and cellular stress responses [16,32]. Within estrogen biotransformation, anthocyanins and related phenolics appear to tilt Phase I activity toward CYP1A1-mediated 2-hydroxylation while dampening CYP1B1-mediated 4-hydroxylation, a shift associated with safer metabolite profiles [1,9]. Downstream, COMT-dependent O-methylation and robust UGT/SULT conjugation expedite clearance, lowering effective estrogenic load at receptors [9,31]. The clinically observed increase in 2-hydroxyestrone:16α-hydroxyestrone with blueberry intake is consistent with this enzymatic rebalancing and provides a mechanistic biomarker that can be monitored in trials or practice [31]. Receptor-level effects are nuanced: weak agonism at ERβ with relative antagonism at ERα has been proposed for certain metabolites, a profile with potential benefits in vasomotor symptoms and tissue-specific risk reduction [5,7,28].

**Insulin Sensitivity and Glucose Metabolism:** Multiple pathways underlie glycemic benefits [11,33]. Anthocyanins enhance peripheral glucose uptake through AMPK activation and improved insulin receptor signaling [3,11,34–35]. Canonical downstream events include IRS-1/PI3K/AKT signaling and GLUT4 translocation in skeletal muscle and adipose tissue, yielding greater insulin-stimulated glucose disposal. Indirect effects include improved mitochondrial efficiency, reduced ER stress, and dampened NF-κB activity, which collectively alleviate insulin resistance [16,34–35]. In the liver, anthocyanin-rich interventions have been associated with down-regulation of gluconeogenic enzymes (PEPCK, G6Pase) and improved hepatic insulin signaling, aligning with trial-level reductions in fasting glucose and HOMA-IR [3,35–36].

Inhibition of α-amylase and α-glucosidase blunts postprandial glycemia and supports insulin sensitivity [36]. Adipokine remodeling—higher adiponectin, improved leptin sensitivity—links berry intake to better hepatic insulin signaling and reduced lipotoxicity [36,37]. Over time, these changes feed forward into improved β-cell function and decreased ectopic fat, aligning with trial evidence in prediabetes and metabolic syndrome [35,37–40]. Epigenetic influences on insulin-signaling genes (histone acetylation, miRNA expression) have been observed with blueberry bioactives, offering a mechanistic bridge between short-term signaling and longer-term phenotype [41].

At the cellular level, anthocyanins promote AMPK activation, downstream ACC phosphorylation, and GLUT4 translocation in skeletal muscle and adipose tissue, thereby enhancing insulin-independent glucose disposal and improving insulin receptor substrate signaling under insulinized conditions [11,34–36]. Inhibition of α-amylase/α-glucosidase tempers postprandial excursions, reducing glucotoxic and lipotoxic signaling that otherwise propagate endocrine dysfunction [36]. Anti-inflammatory actions (NF-κB constraint, reduced cytokines) reduce serine phosphorylation of insulin signaling intermediates and help normalize adipokine profiles (↑adiponectin, ↓leptin resistance), which further supports HOMA-IR improvements seen in trials [16,33–35,38,37]. These convergent mechanisms explain why modest changes in diet can translate to measurable metabolic and hormonal benefits over weeks to months [35,36,39].

**Stress-Hormone Regulation:** Berry constituents modulate the hypothalamic–pituitary–adrenal (HPA) axis via effects on steroidogenesis and neural resilience. Specific flavonoids inhibit 11β-HSD1, reducing local cortisol activation in adipose and hepatic tissues [15,42–43]. Antioxidant/anti-inflammatory actions in hypothalamic and pituitary regions support HPA homeostasis [1,17].

Sleep and circadian influences—including endogenous melatonin in some cultivars and neuromodulatory effects of flavonoids—may improve diurnal cortisol patterns and sleep architecture, with timing of intake emerging as a variable of interest [43–45]. Improvements in perceived stress and mood commonly accompany cortisol normalization in supplementation trials, suggesting psychoneuroendocrine relevance beyond metabolic endpoints [15,17,43].

Berry bioactives modulate the HPA axis at multiple tiers: peripheral regulation via 11β-HSD1 inhibition reduces tissue cortisol regeneration; central effects mitigate oxidative and inflammatory stress within hypothalamic and pituitary circuits; and circadian alignment influences the cortisol awakening response and diurnal slope [15,42–45]. Preliminary chrono-nutrition data suggest that morning consumption may better synchronize cortisol rhythms in some individuals, whereas evening intake could support sleep and next-day stress reactivity—an area ripe for targeted trials [44,45]. The net outcome is not simple suppression but homeostatic recalibration toward physiological amplitude and timing, aligning with observed improvements in mood and stress resilience [15,17,42–44].

**Thyroid Hormone Function:** Emerging evidence suggests effects on thyroid synthesis, transport, and metabolism, although clinical relevance remains to be defined [46]. Given the gland's oxidative vulnerability, antioxidant support may be protective, with potential impacts on autoimmune processes [30] and hormone-binding proteins (e.g., thyroxine-binding globulin, transthyretin) [29]. Additional mechanistic candidates include modulation of deiodinase activity (D1/D2/D3) and iodide handling within the follicular lumen; preclinical signals require human confirmation [26–27,46].

Emerging work indicates interactions with deiodinases (DIO1/2/3) that govern peripheral T4→T3 conversion and T3 inactivation, although clinical significance remains to be clarified [38]. Antioxidant support may protect thyroid peroxidase and limit autoantigen presentation in autoimmune contexts, complementing observed reductions in thyroid antibodies in small pilot studies [29-30,46]. Transport dynamics involving transthyretin and thyroxine-binding globulin could modulate free hormone fractions under certain dietary patterns, reinforcing the need for controlled human studies to delineate dose and context [29].

## Clinical Evidence and Human Studies

**Reproductive Health and Menopause:** Randomized trials indicate benefits for menopausal symptoms and hormone markers. In postmenopausal women, daily freeze-dried blueberry (25 g) over 12 weeks reduced hot-flash frequency/severity and improved sleep and mood, alongside shifts toward favorable estrogen metabolite ratios (higher 2-hydroxyestrone:16α-hydroxyestrone) [27,31]. A crossover study in perimenopausal women found raspberry extract (≈200 g fresh equivalent/day for 8 weeks) improved symptom burden, inflammation, and oxidative stress [47,32]. Cohort data further associate higher berry intake with lower rates of hormonal disturbances and reproductive disorders over long-term follow-up [48]. Overall intervention characteristics and outcomes are summarized in Table 2.

Beyond symptom scales, studies increasingly include biochemical panels (estrone/estradiol metabolites, SHBG), vascular endpoints, and bone-turnover markers to capture broader endocrine effects [28,31]. Sleep quality indices and mood inventories often improve in parallel, consistent with HPA-axis modulation and circadian support [43–44]. Although formulations vary (whole fruit, powders, extracts), benefits have been most consistent when interventions deliver standardized anthocyanin/ellagitannin doses and are aligned with habitual dietary patterns. Adverse events are rare and mild, predominantly gastrointestinal, reinforcing feasibility for midlife women [30].

The menopausal RCTs highlight practical design features that refine interpretation: dose forms (whole fruit vs. powder), placebo composition (isosweet but

polyphenol-free), and compliance checks (anthocyanin metabolites in urine) are critical to attributing effects to berry bioactives [27,31,32]. Reported improvements in vasomotor symptoms, sleep, and mood co-occurred with shifts in estrogen metabolite ratios and systemic inflammatory markers, supporting a biologically coherent mechanism chain from intake to clinical outcomes [27,31,32]. Importantly, response heterogeneity aligns with hypothesized microbiome and genetics influences, indicating a role for personalized dosing or concurrent microbiome-supportive strategies [23–25,28,31].

**Table 2.** Human evidence snapshot: interventions and key outcomes.

| Indication/Population | Intervention (typical) | Primary outcomes | Adverse events |
|---|---|---|---|
| Peri/post menopause | Blueberry/mixed-berry 150–250 g/d (8–16 w) [27,31–32,43–44,48] | ↓Hot flashes; ↑sleep/mood; ↑2-OHE1:16α-OHE1 [27,31–32,43–44,48] | Rare, mild GI [27,31–32,43–44,48] |
| Prediabetes / IR | Blueberries ~150–200 g/d (8–24 w) [35,36,38–40] | ↓HOMA-IR; ↑OGTT indices; ↓inflammation [35,36,38–40] | Rare [35,36,38–40] |
| Metabolic syndrome | Blueberries 200 g/d (12–24 w) [39–40,35] | ↑Insulin sensitivity; ↓visceral adiposity [39–40,35] | Rare [39–40,35] |
| Hypertension / endothelial dysfunction | Anthocyanin-rich mixes (8–12 w) [43,46–47] | ↓SBP/DBP; ↑FMD; ↓renin/aldosterone [43,46–47] | Rare [43,46–47] |
| Cognition (older adults) | Blueberry powder ~24 g/d (12–16 w) [1,10,41–44] | ↑Executive function/memory; ↓cortisol; ↑BDNF [1,10,41–44] | Rare [1,10,41–44] |
| Autoimmune thyroid (pilot) | Blueberry extract (12 w) [26,30,46] | ↓TPO/Tg antibodies [26,30,46] | Nonserious [26,30,46] |

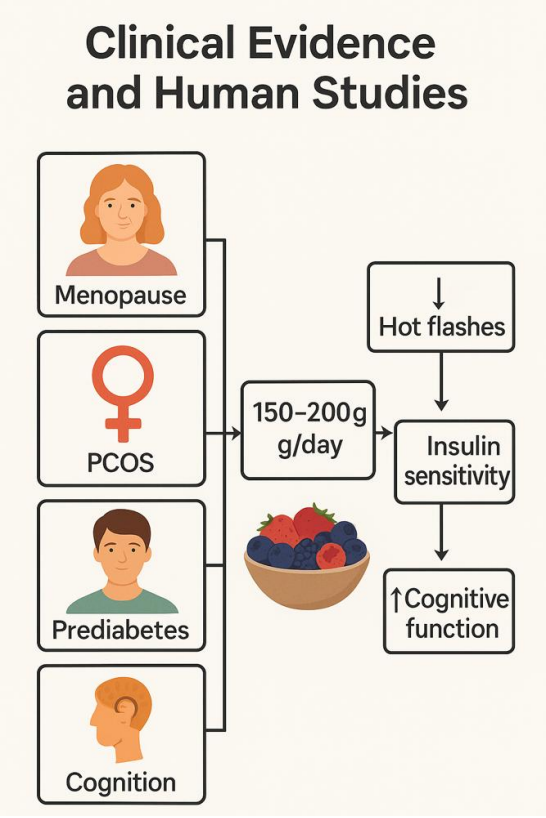



**Figure 2**: Clinical evidence of blueberries and raspberries in human studies. Interventions of 150–200 g/day improve outcomes across menopause, PCOS, prediabetes, and cognition.

**Metabolic Health and Diabetes:** Evidence from randomized trials supports improved insulin sensitivity and metabolic markers. In prediabetes, 150 g fresh blueberries daily for 6 months improved HOMA-IR, reduced inflammation, and enhanced β-cell function [35,38], with concomitant increases in adiponectin and improvements in leptin signaling [45]. A meta-analysis of 15 trials reported consistent gains in glycemic control and insulin sensitivity, with dose-responsive effects [36,39]. Trials increasingly employ multiple endpoints—fasting insulin/glucose, OGTT-derived indices (Matsuda), HbA1c, continuous glucose monitoring for glycemic variability—to triangulate efficacy [35–36,40]. Subgroup analyses suggest larger effects in individuals with higher baseline insulin resistance and in those with diets low in other polyphenol sources [11,36]. Adherence appears facilitated by palatability and flexible delivery (fresh, frozen, powder), with minimal adverse events reported [30]. Dietary displacement effects (e.g., berries replacing refined desserts) may further contribute to net improvements and should be tracked in future designs.

In prediabetes and metabolic impairment, trials consistently report HOMA-IR improvements and favorable adipokine changes after 8–24 weeks, with larger effects at ≥150 g/day fresh equivalent and with intact berry matrices [35,36,38–39]. While few studies employ euglycemic clamps, convergent improvements in oral glucose tolerance, fasting insulin, and surrogate indices reinforce translational relevance [34–36]. Modest yet significant weight-neutral benefits imply that endocrine effects are not merely secondary to weight loss but reflect direct actions on insulin signaling and inflammation [30,35,38,37]. Longer durations will help clarify whether early hormonal shifts predict incident diabetes risk reduction, as suggested by cohort findings [11,33,36].

**Cardiovascular Health and Blood Pressure:** Cardiometabolic benefits appear partly hormone-mediated. In mild hypertension, mixed berry interventions reduced systolic/diastolic blood pressure and improved endothelial function [43,46–47], alongside reductions in renin and aldosterone [15,34–35], consistent with improved vascular tone and risk profiles [36,43,48]. Flow-mediated dilation and pulse-wave velocity measurements complement biochemical markers (nitric oxide metabolites, endothelin-1), indicating improved endothelial signaling. Lipid-related changes—modest LDL reduction and increased HDL functionality—have been noted in some cohorts and may be secondary to improved insulin sensitivity and inflammation control [16,39–40].

Mixed-berry interventions demonstrate reductions in systolic/diastolic pressures and improvements in flow-mediated dilation, coupled to lower plasma renin and aldosterone, consistent with beneficial modulation of the renin-angiotensin-aldosterone axis [43,39,40]. Endothelial function gains may stem from improved nitric oxide bioavailability, reduced oxidative stress, and dampened endothelin signaling—mechanistic paths that intersect with stress-hormone regulation and insulin signaling [16,42,45,40]. Prospective data linking anthocyanin intake to lower cardiovascular events provide population-level support for these endocrine-vascular interactions [48,39].

**Cognitive Function and Neuroprotection:** Blueberry supplementation (24 g powder/day, 16 weeks) improved memory/executive function in older adults, lowered salivary cortisol, and normalized diurnal rhythms [1,42–44], with increases in BDNF [10,41] and supportive neuroimaging evidence of enhanced activation and connectivity in cognitive networks. Cognitive benefits likely integrate vascular improvements (neurovascular coupling), reduced neuroinflammation, and HPA-axis stabilization. Observed effects on sleep continuity and subjective stress add ecological validity and may enhance adherence in aging populations.

Cognitive trials report improvements in executive function and memory alongside reduced salivary cortisol

and elevated BDNF, connecting stress hormone recalibration with neuroplasticity mechanisms [1,15,42,45,41]. Neuroimaging evidence of increased activation and strengthened connectivity in memory-related circuits suggests that polyphenol metabolites reach the brain in behaviorally meaningful concentrations [1,17,42]. Because sleep quality mediates both HPA activity and cognition, the sleep-supportive signals observed with berry intake plausibly contribute to cognitive gains, warranting future trials that co-measure sleep, cortisol, and cognition over longer horizons [15,44,45].

**Dosing, Matrix, and Timing Considerations:** Interventions that deliver roughly 150–250 g fresh berries/day (or equivalent powders standardized to anthocyanin/ellagitannin content) appear sufficient for endocrine-relevant effects in many cohorts [19,35–36,30]. Co-ingestion with mixed meals does not abolish benefits and may improve gastrointestinal tolerance; limited data suggest evening intake can favor sleep and cortisol rhythm endpoints, while pre-exercise intake may accentuate glycemic and vascular responses [43–44]. Processing choices—freeze-dried powders, frozen whole fruit—offer shelf-stable options without large potency penalties when products are quality-controlled [4,19].

## Specific Applications in Hormone-Related Conditions

**Polycystic Ovary Syndrome (PCOS):** Pilot data in PCOS suggest raspberry intake can improve insulin sensitivity and reduce androgen excess. Twelve-week raspberry extract (~300 g fresh equivalent/day) lowered fasting insulin and HOMA-IR, reduced total/free testosterone, increased SHBG, and improved menstrual regularity and hirsutism scores [20,40,49]. Decrements in CRP and IL-6 highlight anti-inflammatory contributions [16,49]. Exploratory signals for LH/FSH ratio normalization and improved ovulatory frequency have been reported, aligning with insulin-lowering effects and potential direct actions on ovarian steroidogenesis. Pragmatically, pairing berry intake with resistance training and fiber-rich meals may amplify improvements in insulin dynamics and satiety.

**Perimenopause and Menopause:** Combined blueberry–raspberry interventions in perimenopause yielded clinically meaningful reductions (≈40%) in moderate-to-severe hot flashes over 16 weeks, with better sleep and mood [2,27,44,50]. Estrogen metabolism shifted toward protective profiles and bone turnover and cardiometabolic markers improved [28,48]. Symptom improvements appear within 6–8 weeks in many trials, with additional gains by 12–16 weeks; durability beyond the intervention period remains an open question meriting longer follow-up. Given inter-individual variability, incorporating simple symptom diaries and, where feasible, urinary estrogen-metabolite ratios could tailor dosing and timing.

**Metabolic Syndrome and Diabetes:** In a 24-week randomized trial (n=400), fresh blueberries (200 g/day) or equivalent powder improved insulin sensitivity; adiponectin increased and leptin resistance decreased, with favorable body-composition changes, particularly in visceral adiposity [3,11,33–36,38–40,49]. Anti-inflammatory shifts (e.g., lower TNF-α, IL-6) paralleled hormonal improvements. Pragmatically, integrating berries into breakfast or post-exercise snacks may amplify glycemic and recovery benefits while supporting adherence. Continuous glucose monitoring sub-studies could clarify acute glycemic variability effects and inform individualized recommendations.

**Thyroid Disorders:** Preliminary data in subclinical hypothyroidism show modest TSH improvements and significant declines in TPO and thyroglobulin antibodies after blueberry extract over 12 weeks, suggesting potential utility in autoimmune thyroiditis; larger controlled trials are needed to confirm efficacy and define

dosing. Given possible interactions with iodine status and autoimmune activity, future trials should stratify by baseline thyroid autoantibody titers and selenium intake [26–27,4630].

Pilot findings of reduced thyroid autoantibodies with blueberry supplementation are hypothesis-generating and align with anti-inflammatory and redox support in thyroid tissue; however, effects on TSH, fT4, and fT3 are modest and variable [26,46,30,29–]. Until larger trials report, pragmatic guidance is to position berries as adjunctive nutrition rather than replacement therapy, with attention to medication timing and consistent intake to avoid confounding of thyroid function tests [46,30,29–40].

**Bioavailability and Metabolism:** Absorption and distribution: Anthocyanins exhibit low apparent bioavailability with plasma peaks at 1–2 h and rapid clearance by 4–6 h. However, metabolites and tissue deposition may better reflect biological activity [4,13]. Microbiota-derived products, particularly urolithins from ellagitannins, likely mediate a substantial portion of endocrine effects and vary with gut community composition [21,23–25]. Transporters (e.g., OATPs) may shape tissue targeting, including endocrine organs [14,29]. Food matrix and co-ingestion (fat, protein) can alter micellarization, intestinal stability, and first-pass metabolism, suggesting opportunities to optimize delivery with meals or encapsulation technologies [19,51–52]. Sustained-release formulations and microencapsulation have been explored to improve stability and distal-gut delivery, with early signals of enhanced metabolite production and glycemic effects [19,52].

**Tissue Distribution and Target-Organ Effects:** Animal studies indicate accumulation in reproductive tissues, liver, and brain—sites central to endocrine regulation. Transplacental transfer has been observed, warranting careful study of pregnancy/lactation use. Blood–brain barrier permeability enables direct hypothalamic and pituitary actions, aligning with observed HPA and circadian effects. Hepatic concentrations can influence Phase I/II enzyme activity, enhancing steroid clearance. Within ovarian and adrenal tissues, polyphenols may modulate steroidogenic enzyme expression (e.g., CYP17A1, aromatase), though human confirmation is pending [7–8,53]. Regional adipose-tissue effects—particularly in visceral depots—may also be relevant given depot-specific 11β-HSD1 activity and adipokine secretion patterns [15,37].

**Elimination and Clearance:** Elimination primarily occurs via glucuronidation and sulfation with urinary and biliary excretion. Enterohepatic recycling may prolong effect duration. Genetic polymorphisms in conjugating enzymes (e.g., UGTs) likely contribute to inter-individual variability in endocrine outcomes. Metabotype-specific differences in urolithin production and conjugation can meaningfully alter exposure–response relationships, emphasizing the promise of personalized approaches [23–25,51,54].

Rapid glucuronidation and sulfation favor urinary and biliary excretion, yet enterohepatic cycling extends exposure to colon microbiota, enabling continued generation of small phenolics with endocrine activity [4,12–14]. Genetic polymorphisms in UGTs/SULTs and microbiome differences in ellagitannin and urolithin pathways explain why identical doses can yield divergent plasma and urinary signatures and, ultimately, divergent endocrine effects [21–25,29]. In practice, this heterogeneity argues for response-based titration and, potentially, future companion diagnostics to guide dosing [23–25].

## Safety Considerations and Contraindications

**General Safety:** Berries have an excellent safety record with high tolerability in clinical studies. Allergic reactions are uncommon but possible via cross-reactivity. Antioxidant-rich interventions should be coordinated with

oncologic care when therapies rely on oxidative mechanisms. Long-term and high-dose studies to date indicate wide safety margins. Gastrointestinal symptoms (bloating, stool softening) may occur with rapid increases in intake due to fiber and polyol content; gradual titration mitigates these effects. Oxalate content is moderate and generally compatible with typical intakes; patients with recurrent calcium oxalate nephrolithiasis should individualize intake with clinical guidance.

**Drug Interactions:** Potential interactions include potentiation of antithrombotic therapy via salicylates/platelet effects [30]; modulation of CYP enzymes relevant to hormone therapy or oral contraceptives [55–56]; and additive glucose-lowering with antidiabetic drugs necessitating monitoring and possible dose adjustments [35,38]. Thyroid hormone replacement should be taken on an empty stomach, separated from fiber-rich meals to avoid absorption interference—a general principle that applies to berry-containing breakfasts.

Clinically meaningful interactions are uncommon, but vigilance is warranted where polyphenols may influence CYP activity or UGT/SULT conjugation relevant to hormone therapy or contraceptives; patients should report changes in bleeding patterns or symptom control that coincide with major diet shifts [55,56]. For those on antidiabetic medications, berry-induced improvements in glycemia may necessitate monitoring to avoid hypoglycemia, particularly when other lifestyle interventions are initiated concurrently [35,38]. Individuals on anticoagulants or antiplatelet agents should maintain a consistent intake pattern and follow routine monitoring protocols given modest salicylate exposure and potential effects on platelet function [9,30].

**Practical Implications (medical).** For clinicians, blueberries and raspberries can be positioned as adjunct dietary therapy for endocrine-related concerns. In peri/postmenopausal women, recommend ~150–200 g/day whole berries (or standardized freeze-dried equivalent) to support estrogen metabolism and symptoms (sleep, mood, vasomotor). In insulin resistance/PCOS, integrate daily berries within a low-added-sugar pattern to enhance insulin sensitivity (AMPK/IR signaling) and complement lifestyle or metformin; monitor fasting glucose/insulin, HOMA-IR, HbA1c (≥8–12 weeks). For stress-related dysregulation, pair intake with sleep hygiene and track diurnal cortisol or validated sleep scales. Document mechanistic biomarkers where feasible (e.g., SHBG, estrone/estradiol ratios, lipid peroxidation/antioxidant assays) to align with functional food evaluation. Safety: generally well tolerated; consider berry allergy, high-oxalate history, GI sensitivity, and carbohydrate goals (use unsweetened forms). Potential additive effects with α-glucosidase inhibitors; evidence for extracts vs whole fruit remains limited—prefer whole-food first, then consider standardized products in dietitian-supervised plans.

**Special Populations**: Routine dietary intake is considered safe in pregnancy and lactation, though high-dose supplements warrant caution pending additional data [57]. Pediatric use should avoid concentrated supplements until endocrine effects are better characterized [58]. Older adults may benefit given age-related endocrine shifts, but polypharmacy requires vigilance [9,45]. Individuals with estrogen-sensitive cancers should seek a clinician's guidance regarding dose/form. For all groups, whole-food approaches are preferable to high-dose isolates unless supervised in research or clinical protocols.

**Abbreviations:** AMPK: AMP-activated protein kinase; BDNF: Brain-derived neurotrophic factor; CYP: Cytochrome P450 enzyme; COMT: Catechol-O-methyltransferase; DBP: Diastolic blood pressure; DIO1/2/3: Deiodinase isoenzymes type 1/2/3; ERα/ERβ:

Estrogen receptor alpha/beta; ER: Estrogen receptor; FMD: Flow-mediated dilation; FSH: Follicle-stimulating hormone; GLP-1: Glucagon-like peptide-1; GLUT4: Glucose transporter type 4; GI: Gastrointestinal; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HPA: Hypothalamic–pituitary–adrenal (axis); HPLC-DAD: High-performance liquid chromatography with diode-array detection; IL-6: Interleukin-6; IRS-1: Insulin receptor substrate 1; LH: Luteinizing hormone; NO: Nitric oxide; NF-κB: Nuclear factor kappa-B; Nrf2: Nuclear factor erythroid 2–related factor 2; OGTT: Oral glucose tolerance test; OATPs: Organic anion transporting polypeptides; PCOS: Polycystic ovary syndrome; PEPCK: Phosphoenolpyruvate carboxykinase; PI3K: Phosphoinositide 3-kinase; RA: Rheumatoid arthritis (from example); RCT: Randomized controlled trial; SBP: Systolic blood pressure; SCFA: Short-chain fatty acid; SERM: Selective estrogen receptor modulator; SHBG: Sex hormone–binding globulin; SULT: Sulfotransferase; Tg: Thyroglobulin; TNF-α: Tumor necrosis factor alpha; TPO: Thyroid peroxidase; TSH: Thyroid-stimulating hormone; UGT: UDP-glucuronosyltransferase.

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