semaine

DESIGN PHILOSOPHY:

The Daily Hormone Balance

Perspective

- Changes in modern diets and activity levels have significantly increased the rates of insulin resistance in the population at large, as well as comorbidities including hypertension
- 50% of adult women in the U.S. have either hypertension or prehypertension[1]
- Insulin resistance and hypertension are significant comorbidities[2]
- Insulin resistance can significantly impact fertility during childing-bearing years[3]
- During perimenopause and menopause, rates of insulin resistance increase significantly[4]
- Metabolic dysregulation and insulin resistance are physiologically stressful and impose significant burdens on patient lives:
  - » Increased levels of acne and breakouts, which result in decreased socialization and reduced mental wellbeing[5]
  - » Increased likelihood of PCOS and menstrual irregularity[6]
  - » Higher probability of experiencing anxiety and depression[7]
  - » Fatigue and reduced energy[8]
  - » Increased chronic inflammation resulting in poor long-term health outcomes[9]
  - » Increased blood pressure and hypertension[10]
- Most "hormone balancing" supplements on the market focus on affecting sex hormones. These include plant extracts like black cohosh, dong quai, and maca. All of these are believed to work primarily through influencing sex-hormone levels.
- For many individuals, addressing the underlying metabolic issues is more helpful. Improving insulin sensitivity can:
  - » Decrease acne and breakouts significantly[11]
  - » Alleviate depression and mood changes[12]
  - » Improve chronic inflammation and reduce long-term risks such as heart disease[13]
  - » Improve menstrual regularity and androgen balance[14]
- Many women prefer to use natural as opposed to pharmacological products; failing to engage with this population does them a disservice
- The symptoms (breakouts, low energy, irregular periods, mood changes) that are linked with insulin resistance and prehypertension are most commonly perceived by the public to be issues with "hormone balance"

The Daily Hormone Balance shows it is possible to rationally design a product that supports multiple physiological factors linked with "hormone balance," and that does so in a safe manner. This product supports metabolic hormones during reproductive years and beyond.

What the Daily Hormone Balance Is Not

- **Not alternative medicine.** The Daily is grounded in science and medicine. It relies on clinical data, and it is designed to be supported by rigorous clinical trials.
- **Not a cure.** The Daily does not cure diseases and does claim to, but rather provides support for individuals struggling to eat healthily and exercise.
- **Not a quick fix.** Changes to diet and exercise are the best approaches to hormone balance, and The Daily is designed to be a supportive addition to lifestyle changes.

Semaine Health Co. Philosophy

- Rooted in a patient- and advocacy-focused approach with deep relationships, especially in the endometriosis community
- Focused on continuous engagement with medical professionals to guide product development and provide useful information to customers
- Committed to using clinical trials to validate claims. Results from the pilot study are included in this report

Product Profile for The Daily Hormone Balance

Design Objectives:

- Provide key vitamins that are linked to long-term health and at levels that are supported by epidemiological studies (B vitamins)
- Address nutritional deficiencies that have been linked to insulin resistance (magnesium and zinc)
- Provide support for improved blood sugar and reduced insulin resistance (berberine)
- Address hypertension, a key comorbidity with insulin resistance (grape seed extract)
- Address mood (passionflower)
- Designed to support health in pre-/peri-/postmenopausal age ranges

Product Formulation:

B-complex: B1, B6, B9, B12

Rationale:

- Provide sufficient folate if pregnancy should occur
- Support healthy brain aging
- B-complex (B1/B6/B9/B12) has the potential to support improved homocysteine levels and reduced inflammation
- B-complex supplementation has been shown to improve mood, especially for people with PMS or PMDD

Safety:

- Within recommended FDA tolerable upper limits for all ingredients where applicable
- B1: no established upper limit
- B6: FDA upper limit (100 mg for women ages 19+)
- B9: FDA upper limit (1,000 mcg DFE for women ages 19+)
- B12: no established upper limit

Forms and dosage

- B1: thiamine HCl (20 mg)
- B6: pyridoxine HCl (20 mg)
- B9: calcium L-5 methyltetrahydrofolate (680 mcg DFE)
- B12: cyanocobalamin (4 mcg)

Zinc

Rationale: Zinc supplementation has been shown to improve insulin sensitivity and decrease acne.

Safety: Good if within FDA tolerable upper limits (40 mg for women ages 19+).

Form and dosage

- Dosage: 20 mg of elemental zinc
- Form: zinc glycinate monohydrate. Zinc is often very poorly absorbed and can cause GI distress. Using a form with an amino acid attached increases bioavailability and decreases GI side effects.

Magnesium

Rationale: Changes in dietary habits mean that 45% of Americans are deficient in magnesium.[15] This is associated with hypertension and insulin resistance.[16]

Safety: Excellent if within FDA tolerable upper limit (350 mg for women ages 19+)

Form and dosage

- Dosage: 19 mg elemental magnesium
- Form: Sucrosomial® magnesium. This is magnesium oxide enclosed in a liposomal-type structure. This provides a high level of elemental magnesium while increasing biovailability and avoiding the GI issues commonly associated with straight magnesium oxide.

Berberine

Rationale: Berberine has been widely used in Asia to help with insulin resistance. Several recent RCT intervention studies have shown an improvement in PCOS and in HOMA-IR.

Safety: Excellent safety profile, and the form selected minimizes total dose. At higher doses (>1.5 g/day) most common side effects are GI related.

Form and Dosage:

- Dosage: 80 mg of berberine/day (from a 250 mg dose of berberine Phytosome)
- Form: berberine Phytosome. Optimized for bioavailability by enclosing it in a fat and protein structure. This increases bioavailability ~10X on a molar level.
- Rationale: Most intervention studies use 500 mg to 1.5 g of berberine HCl per day, with the most common side effects reported as GI. Our dose is equivalent to 800 mg of berberine HCl while minimizing raw extract levels.

Grape Seed Extract (GSE)

Rationale: Primarily composed of compounds called proanthocyanidins, GSE is an extremely strong antioxidant. Meta-analysis of many studies has found it effective in hypertension, and this was especially profound in obese subjects or those with metabolic issues.[17,18] GSE has also been shown to help with PMS and mood, likely through its antioxidant behavior.[19]

Safety: GSE has an excellent safety profile

Form and Dosage:

- Dosage: 180 mg
- Form: Enovita®, a standardized extract from Indena. Water extracted and composed of >95% proantho-cyanidins.

Passionflower

Rationale: Passionflower is widely used to help with anxiety and mood changes, and it is shown to reduce inflammation over time. It appears to work by increasing GABA levels in the brain. Mood changes and anxiety are some of the most common symptoms reported and linked to “hormone imbalance.”

Safety: Good; dosages up to 800 mg have been used safely in studies lasting eight weeks. Dosages of 3.5 g+ may be unsafe in short-term use.

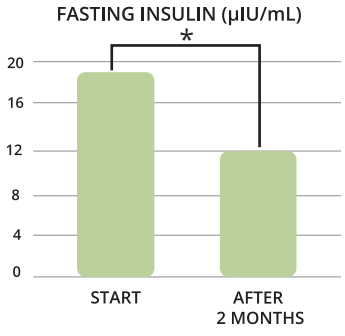
Form and Dosage:

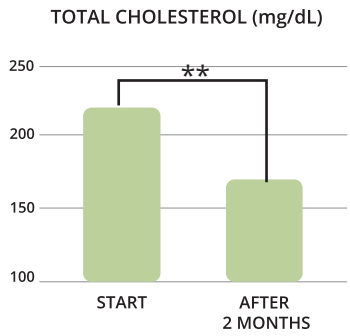
- Dosage: 80 mg (10% of dose used for longer-term trials)
- Form: An ethanol and water extraction from the flower standardized to >4% vitexin.

Pilot Clinical Trial

To help determine the efficacy of the product, an independent third-party-conducted trial was designed and registered at clincaltrials.gov (NCT05328609). This was an observational open-label trial. All participants (n=45) experienced a two-month intervention.

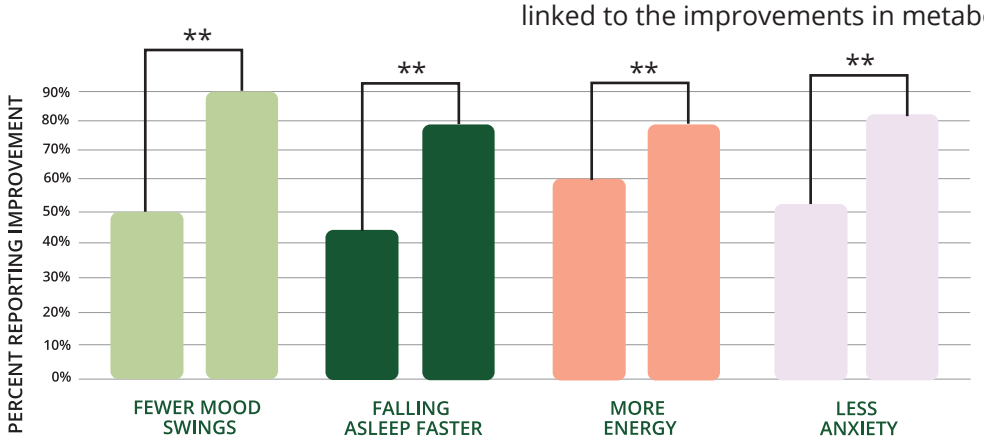
Participants were recruited if they had self-reported changes in mood or mood swings, low energy, food cravings, or difficulty sleeping.





All participants completed a baseline survey about perceived discomfort regarding mood, energy, sleep, and skin as well as an at-home dried-blood-spot test. Participants then completed the perceived discomfort survey throughout the trial and a blood test upon conclusion.

In addition to the improvements in perceived comfort, participants had significant improvements in their lipid profile ($p<.001$) and fasting insulin ($p<0.05$). The average measurements are shown below and suggest that the improvements in perceived comfort are likely linked to the improvements in metabolic state.



CHANGES AFTER **1 WEEK** AND **1 MONTH**

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