

Is there such a thing as “natural Ozempic”?



I recently attended the Integrative Healthcare Symposium (IHS), an annual conference held here in Manhattan. The lectures were informative, but what I really enjoy is reuniting with colleagues and browsing the exhibit hall where supplement manufacturers highlight their latest innovations.

Every year has a fad. Last year it was CBD products; booth after booth featured the latest cannabinoid formulation.

This year, CBD was less prominently featured; it appears that the CBD “gold rush” which spawned numerous small startups, has ebbed, with only large established companies like our sponsor CV Sciences having weathered the intense competition.

In its place was a welter of innovative natural weight loss products drafting on the enormous popularity of GLP-1 drugs like Ozempic, Rybelsus, Wegovy, Mounjaro, and Zepbound.

The use-case for natural GLP-1 agonists is fourfold:

1. For people who are reluctant to take drugs and are seeking natural alternatives

2. For people who have tried Ozempic, Rybelsus, Wegovy, Mounjaro, or Zepbound but have experienced intolerable side effects like severe nausea, constipation or diarrhea
3. For people who can no longer afford the steep costs of weight loss medications (up to \$1200/month) and seek more economical alternatives
4. For people who have attained their weight loss targets with medication and want to avoid rebound weight gain—which averages 70% upon cessation of the drugs

In the past, natural weight loss products were of five major types:

1. Fiber products that gave you a sense of fullness, promoting early satiety
2. Carb-blockers derived from beans that inhibited the breakdown of starchy foods (in the process giving you major flatulence)
3. Speedy natural compounds like citrus aurantium and EGCG with or without caffeine billed as “fat-burners” that mimicked the appetite-suppressing effects of amphetamine drugs
4. Products billed as blood sugar regulators like chromium, gymnema, and berberine
5. Amino acid formulations featuring ingredients like tryptophan or 5-HTP that are said to boost brain levels of serotonin to reduce cravings

I was never much of a fan of these products for weight loss per se, and in fact turned down potentially lucrative deals to endorse them. I just don't think they work that well for shedding pounds. When people don't get results, they become even more demoralized about their prospects for weight loss and give up.

But the popularity and clear efficacy of pharmaceutical drugs has spawned new initiatives to draft on the science of GLP-1 with natural alternatives that harness their modes of action.

Recall that the current weight loss drug revolution was launched when a substance called Exendin-4 was isolated from the saliva of the Gila monster, a venomous lizard that manages to survive in a harsh desert environment. It eats only 5-10 times per year, enjoying a survival advantage via an ability to fast for long periods of time.

This led to the synthesis of a variety of novel diabetes medications based on gut peptides that were found to also induce significant weight loss. Presto! An industry that has propelled companies like Novo Nordisk and Eli Lilly to top stock market valuations with hundreds of billions of dollars of sales.

I considered the potential—and serious downsides—of these drugs in a recent newsletter article: “The End of Obesity?”

One of the most exciting and well-researched natural alternatives harnesses the power of the microbiome to promote improved blood sugar control and leanness. It comes to us from **Pendulum**, a startup seeded with \$150 million of private equity investment.

The antecedent is that we know that metabolism is gut-mediated; the hormones that govern satiety are secreted in the liver and, to some extent, by the intestine. The composition of the microbiome has an impact, not only on breakdown and absorption of the foods we digest, but also on satiety signals that regulate food intake, and thus weight.

For example, transferring stool from an obese human to a normal rat will cause the

rat to consume more food and become obese; there are cases where people who have received therapeutic “fecal transplants” from healthy donors for conditions like life-threatening *C. difficile* infections have been cured of their diarrhea, but have gained unwanted weight because their donors weren’t properly screened for obesity.

Central to these effects is a bacteria called *Akkermansia muciniphila*. Metabolically-healthy individuals harbor plentiful *Akkermansia*; overweight individuals with diabetes or metabolic syndrome have a paucity. A recent article states:

“The mechanisms by which A. muciniphila regulates obesity and glucose levels have not yet been completely elucidated. A previous study showed that A. muciniphila was able to increase thermogenesis and the secretion of glucagon-like peptide-1 (GLP-1) and reduce the expression of proteins involved in adipose cell differentiation, and the gene expression of glucose and fructose transporters in the jejunum, suggesting that A. muciniphila reduces carbohydrate absorption.”

That’s fine in theory, but will supplementation with a probiotic help people improve their blood sugar and carb cravings?

Pendulum performed a study with their proprietary probiotic, which included *Akkermansia* teamed with four other bacterial strains that demonstrated improvements in hemoglobin A1c in diabetics. This study does not, of course, preclude the possibility that *other* commercially-available probiotic formulations can’t perform similarly; many, like Dr. Ohhira’s are capable of generating post-biotics like butyrate which are, at least in part, responsible for the blood sugar and satiety-regulating effects of the Pendulum product.

Akkermansia is touted as an ingredient by lots of companies, but it seems Pendulum is the only company that offers live, viable *Akkermansia*, which is hard to grow and encapsulate because exposure to oxygen kills it. They had to custom-build a multi-million dollar manufacturing facility to produce it under strict anaerobic conditions.

Nonetheless, there are skeptics. Some studies have cautioned that *Akkermansia* excess might be a problem:

“The role of A. muciniphila remains controversial . . . over-colonization of A. muciniphila decreased intestinal mucin content . . . Our findings reveal that excess colonization by A. muciniphila breaks the dynamic balance between mucin secretion and degradation, reduces the thickness of the intestinal mucus layer, and damages the intestinal barrier, which would eventually aggravate the development of colitis and CRC [colorectal cancer]. These results will raise awareness about the safety of A. muciniphila serving as a probiotic.”

Another weight-loss candidate rolled out at IHS was Calocurb, touted as a “patented world-first GLP-1 activating supplement”.

It was developed via a \$20 million innovation grant from the government of New Zealand. A 2022 paper in the *American Journal of Clinical Nutrition* demonstrated that a proprietary extract of New Zealand bitter hops “ . . . suppressed EI [energy intake] and modified the release of hormones involved in appetite and glycemic regulation . . .” in a cohort of healthy-weight men.

An additional study showed Calocurb reduced hunger, food cravings and rebound eating in women undergoing a day-long fast.

It's believed that hops acts as a "bitter brake" on appetite; studies have revealed that, in addition to oral taste buds, there are intestinal taste receptors that respond to bitter substances by secreting appetite suppressing gut peptides like GLP-1.

Finally, at IHS I discovered "HiPhenolic" from OrthoMolecular. It's a combination of hibiscus—traditionally used as a tea to curb high blood pressure—and lemon verbena, teamed with caffeic acid, the green coffee bean extract that has some promising clinicals supporting its weight loss effects (independent of caffeine content).

The proprietary blend of hibiscus and lemon verbena, called Metabolaid® has been found in mice to produce weight loss by triggering thermogenesis (fat-burning); a human trial demonstrated improvements in blood pressure and "a significant reduction of body fat content".

Parenthetically, Yerba Maté tea has been shown to have GLP-1 effects; a small human trial showed *"Yerba Mate supplementation decreased body fat mass, percent body fat and WHR [waist-to-hip ratio]. Yerba Mate was a potent anti-obesity reagent that did not produce significant adverse effects."*

I'm not making any claims for any of the above, having not yet had a chance to field-test them in my medical practice. But they appear to be plausible options for people desiring help losing weight with the tried and true methods of diet and exercise.

One additional innovation that I'll share with you: A speaker at IHS acknowledged the reality that many unsuccessful dieters will succumb to the allure of weight loss drugs. But when prescribing them to her patients, she has them sign a contract, stipulating that they will:

1. Adhere to strict diet guidelines, emphasizing adequate protein to forestall loss of lean muscle mass, and fiber to support an optimal microbiome
2. Engage in regular resistance exercise to preserve muscle
3. Take supplemental nutrients as prescribed to address gaps resulting from decreased food intake
4. Undergo behavior modification to support ongoing healthy lifestyle habits upon cessation of medication once weight loss goals are attained (See recent Wall Street Journal story "There's No Easy Way to Stop Taking Ozempic")

That approach, possibly along with plausible supplements as described above, may be the soundest way to deploy these weight loss drugs, not merely as a quick fix, but as a truly transformational opportunity for the overweight who now constitute a majority of American adults.