Everything You Need to Know about Natural GLP-1 Activators

February 28, 2024

Presenters

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Objectives:

- Understand appetite suppression and the function of GLP-1s
- Evaluate the state of research into natural activators of GLP-1s
- Apply a natural GLP-1 activator in your clinical practice for weight loss, fasting, and transitioning off GLP-1 medications
- Compare side effect profiles for pharmaceutical and nutraceutical GLP-1s

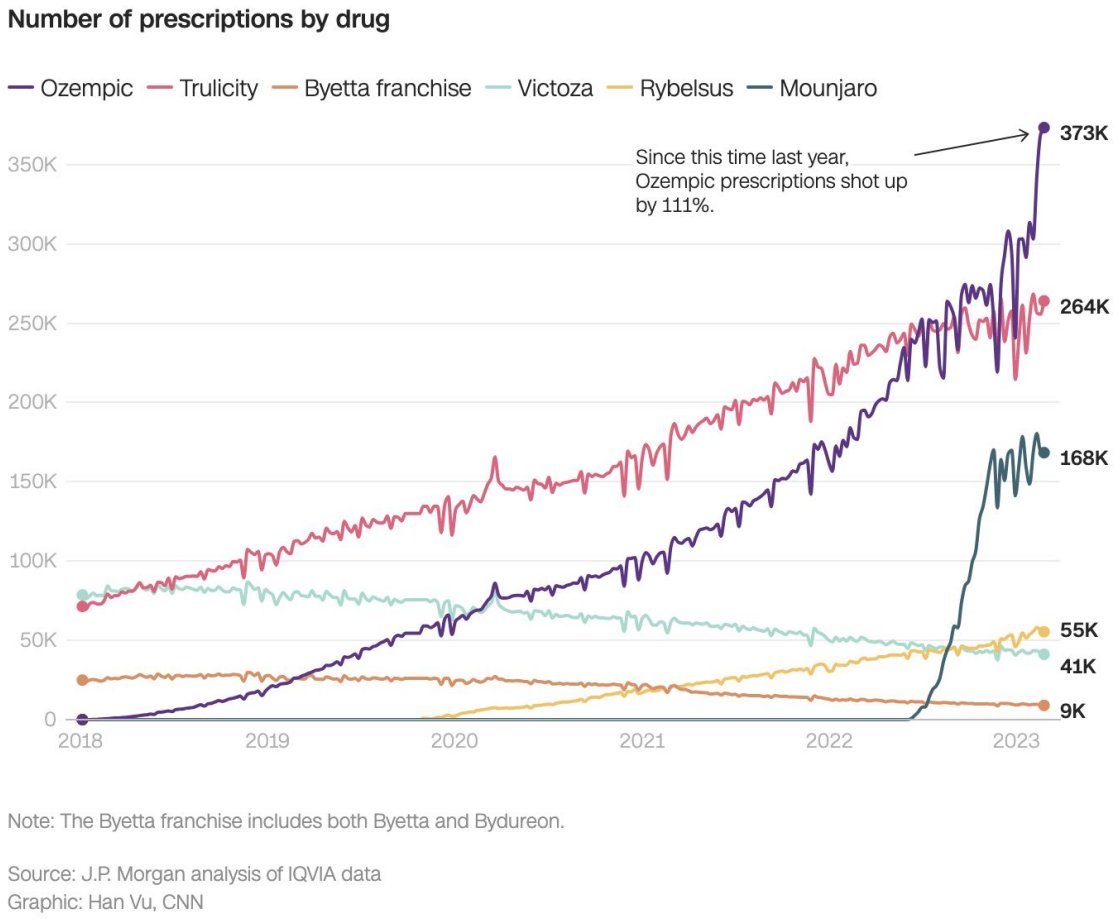
The stage was set for massive disruption.

- 69% of the US population is obese (41.9%) or overweight.
- By 2030, 78% of the population will be obese (50%) or overweight.
- Of those who successfully lose weight, only 20% achieve a degree of long-term success keeping it off - illustrating the enormous difficulty of resisting hunger/ cravings over time. (Rossner et al. 2008)
- Safe, sustainable appetite control is likely the holy grail.

Appetite Control is Key

The Arrival of GLP-1s

- 9M Rxs in 2022
- 30M people by 2030 (9% of the population)
- Jenny Craig is dead after 40 years
- Weight Watchers and Noom now sell it.



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The Opportunity for Root Cause Medicine Practitioners

- Personalization
  - Dosing
  - Prevention and management of side effects (muscle loss, GI distress, and “medically induced malnutrition”)
- Locus of control
- Identifying and exploring viable alternatives and tools to enable successful de-prescribing (avoiding the “Ozempic rebound”)

First-Generation Prescription Weight Loss Medications

Phentermine	Hydrogel	Orlistat	Naltrexone/Bupropion ER (Contrave)	Phentermine/Topiramate ER (Qsymia)
Weight Loss: 3.6%	**Weight Loss**: 2%	**Weight Loss**: 2.8%	**Weight Loss**: 3%	**Weight Loss**: 8.5%
Pros: Short-term effectiveness, increases energy expenditure	**Pros**: Increases fullness, reduces calorie intake	**Pros**: Inhibits fat absorption	**Pros**: Reduces appetite, increases satiety	**Pros**: Significant weight loss, appetite suppression
Cons: Dependency risk, cardiovascular risks	**Cons**: Multiple administrations needed, lower effectiveness	**Cons**: Interferes with vitamin absorption	**Cons**: Not for those with seizure disorders	**Cons**: Birth defects risk, mood monitoring required
Side Effects: Increased heart rate, dry mouth, insomnia	**Side Effects**: Abdominal pain, bloating, nausea	**Side Effects**: Oily spotting, flatulence, urgent bowel movements	**Side Effects**: Nausea, constipation, headache	**Side Effects**: Tingling in hands/feet, altered taste, insomnia

Nutraceuticals

- Problem:
  - Lack of clinical data to support their efficacy and safety
  - Unregulated manufacturing practices
- Numerous lawsuits regarding false claims/advertising and misleading labeling
  - i.e. GOLO, Sensa, Hcg weight loss products
- Lawsuits regarding improper warnings and complications like liver damage
  - Data from Drug Induced Liver Injury Network, between 2003 and 2011, 679 cases of liver injury i.e. Hydroxycut
    - 93 were associated with dietary supplements
      - bodybuilding supplements, weight-loss supplements, other types of supplements

2nd Generation FDA-Approved Weight Loss Medications

- Semaglutide (Wegovy) & Tirzepatide (Zepbound)
- **Background**: Originally developed for T2DM, Semaglutide & Tirzepatide have shown significant efficacy in reducing body weight (15-20% TBWL).
- **GLP-1 and Weight Loss:**
  - Origin: GLP-1 is a hormone released from L cells in the small intestine upon energy intake.
  - Role: Regulates blood sugar levels, satiety and hunger.
- **Mechanisms of Action:**
  - **Delays Gastric Emptying**
  - **Acts on GLP-1 Receptors in the Brain:** Targets receptors in the brain that regulate food intake, cravings, and hunger.

The combined effects on gastric emptying and brain receptors→feel satisfied eating less and reduction of hunger and cravings

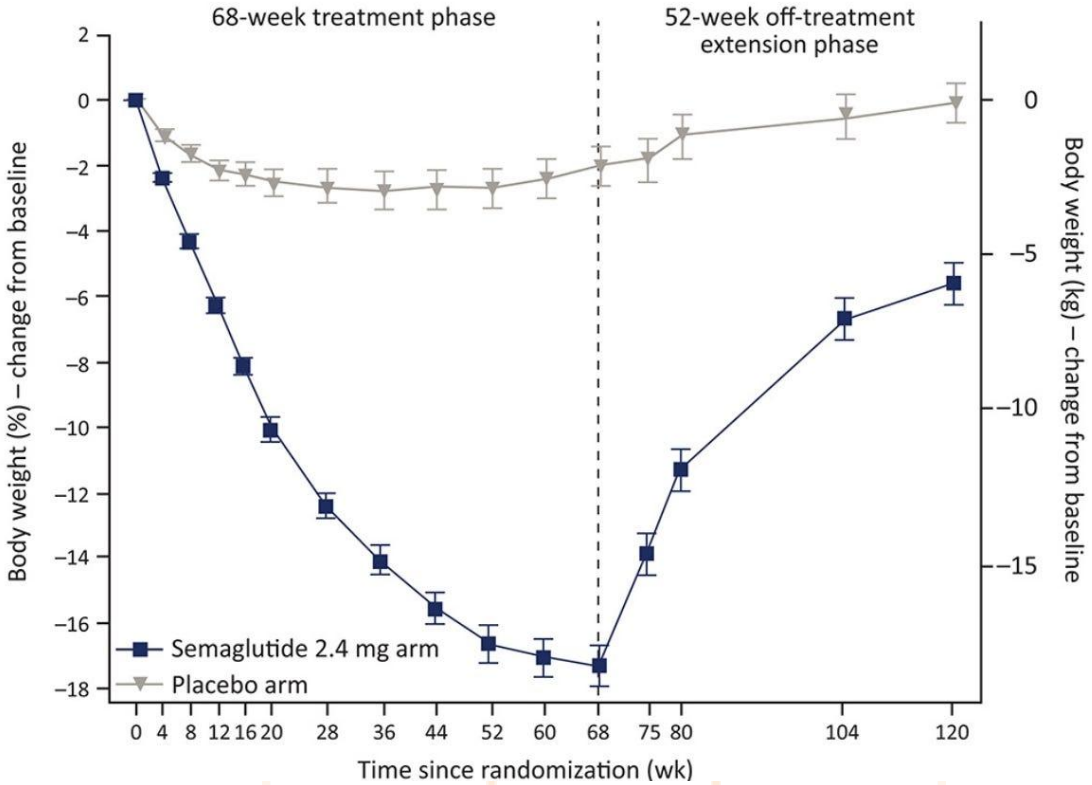
The Promises and Pitfalls of GLP-1s

Medications

Semaglutide (Wegovy) & Tirzepatide (Zepbound)

- Most effective pharmacotherapy on the market

- Things to consider:
  - Most common side effects are GI-related
  - Supply Chain Problems
  - Poor access to expertise
  - High cost



Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension
First published: 19 April 2022 https://doi.org/10.1111/dom.14725

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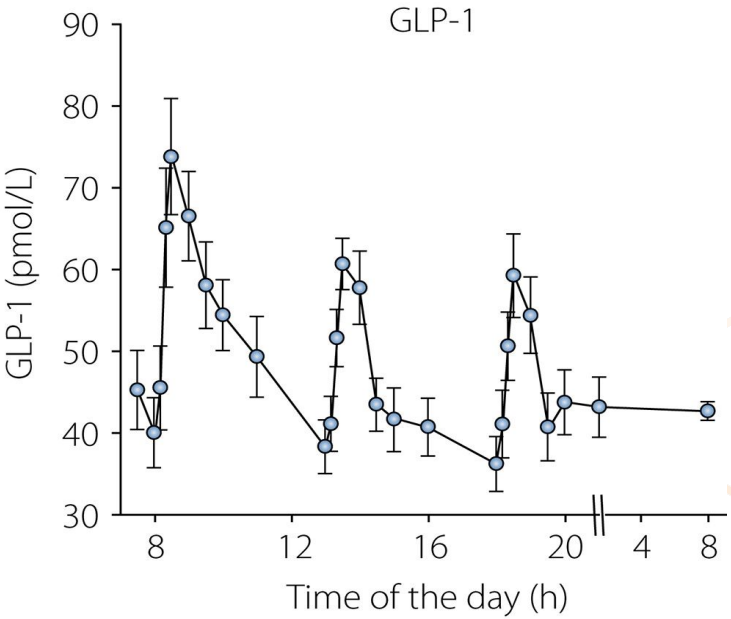
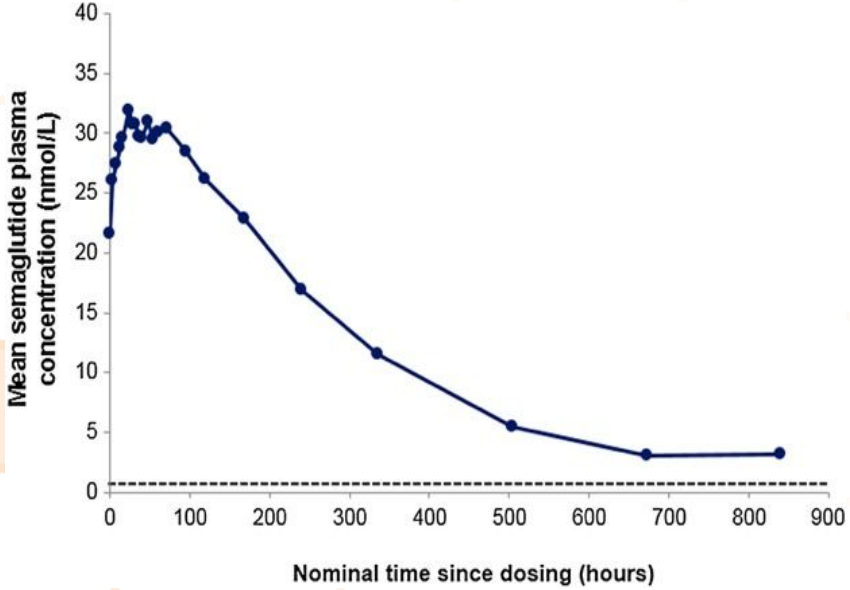
Endogenous GLP-1



Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 secretion in humans: Characteristics and regulation
https://doi.org/10.1111/jdi.13962

Pharmaceutical GLP-1



Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel
https://doi.org/10.1002/jcph.443

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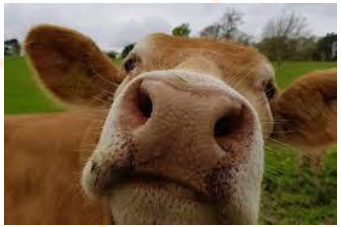
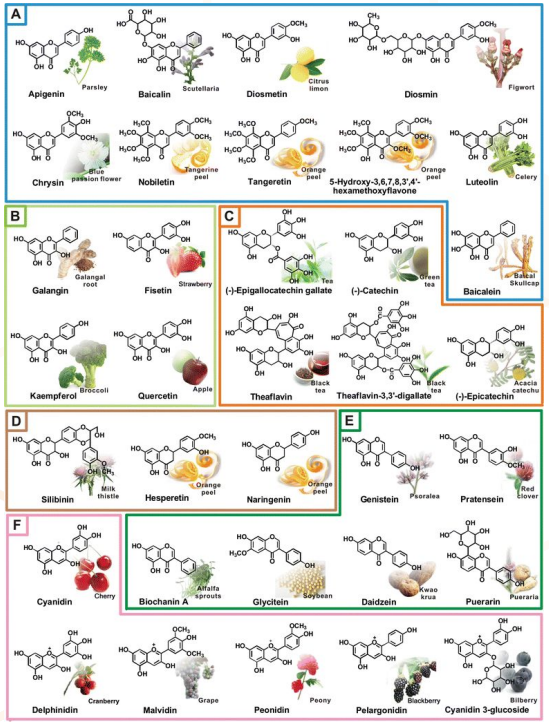
Investigating Natural Approaches Using Bitter Plant Compounds

Why look to plants to modulate appetite?

- 420 million years of evolution in biochemical defenses against herbivores
- Evolution of 100,000 different secondary metabolites in plants, many of which may reduce feeding.
- Nutritional toxicology – animals regulate meal size, meal interval or diet selection to regulate rate at which toxins are consumed and accumulate in the body (Torregrossa & Dearing 2009)
- Many toxins are bitter, and many non-toxic plant secondary metabolites are also bitter.
- Does bitter taste play a role in appetite?





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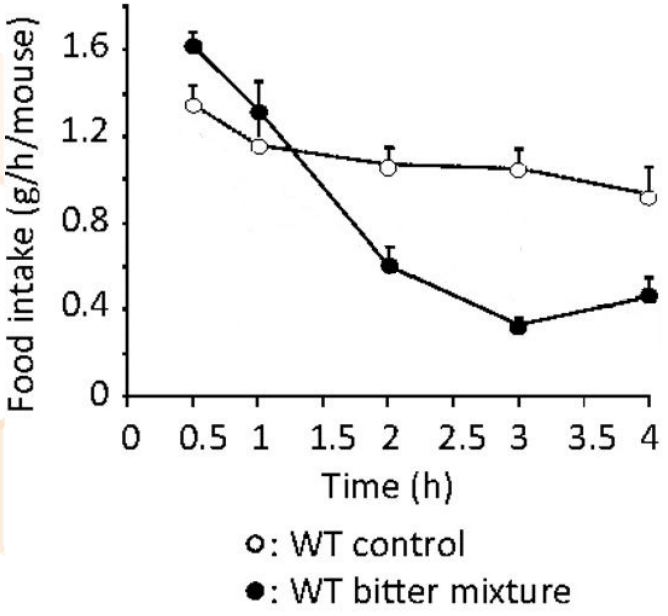
Evidence for Gut Bitterness on Appetite

Time-dependent changes in food intake (g/h per mouse) in mice after gavage of water or Bitter Receptor agonists



Janssen S *et al*. PNAS 2011;108:2094-2099

PNAS

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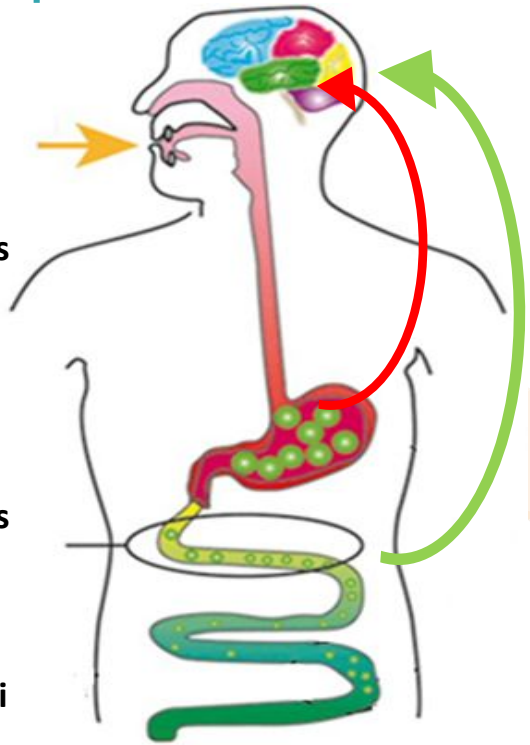
A Bitter Brake on Appetite

Bitter compounds in the stomach = Pro-Appetite response

Bitter compounds in the Small Intestine & Colon trigger Appetite-Supressing effects



The Bitter Brake

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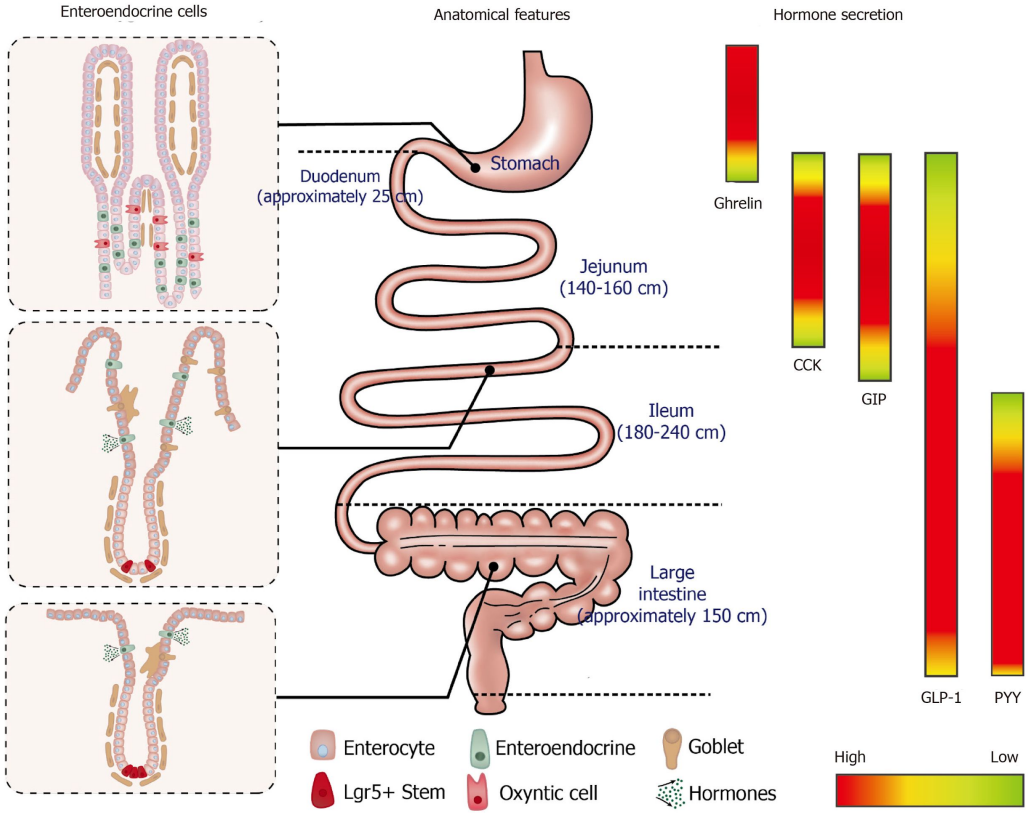
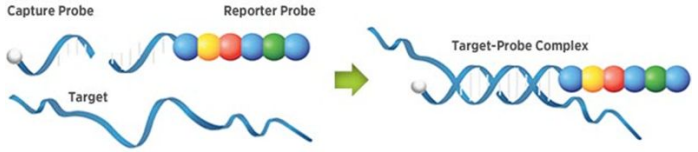


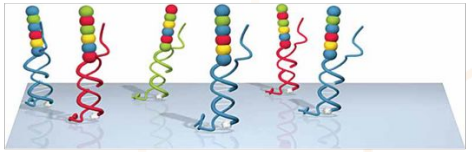
World J Gastroenterol. Jul 7, 2020; 26(25): 3562-3576 Huang WK, Xie C, Young RL, Zhao JB, Ebendorff-Heidepriem H, Jones KL, Rayner CK, Wu TZ. Development of innovative tools for investigation of nutrient-gut interaction. World J Gastroenterol 2020; 26(25): 3562-3576 [PMID: 32742126 DOI: 10.3748/wjg.v26.i25.3562]

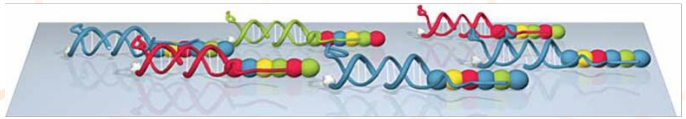
Does the Human Gut Actually have Bitter Taste Receptors?

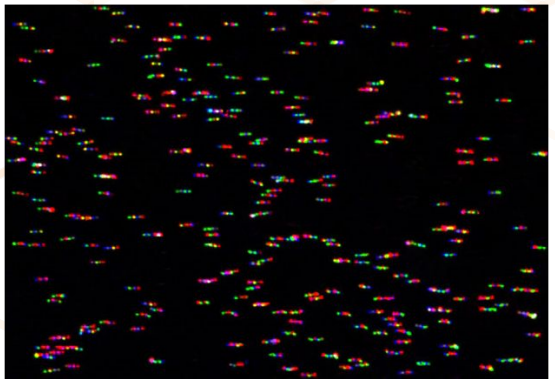
HUMAN BITTER TASTE

- Humans have 25 bitter taste receptors - specialized or focused
- Some are yet to be deorphaned - no known agonists
- Evidence of extra oral expression - found in gut enteroendocrine cells
- Protein assessment impractical due to limited effective antibodies
- Nanostring chosen due to sensitivity for lowly expressed genes - only 1 in 100 cells will be an enteroendocrine cell









Bitter Taste Receptors in the Gastrointestinal Tract

Waitemata District Health Board
Te Wai Awhina
Making a healthy difference to the community

Plant & Food™ Research
Rangahau Ahumāra Kai

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau

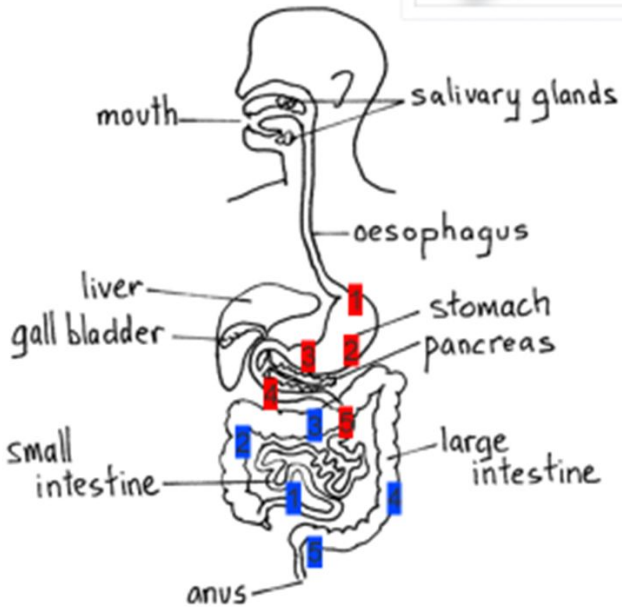
Endoscopic Biopsy Location

Gastroscopy (n=15):

- Stomach:
  - Fundus
  - Body
  - Antrum
- Duodenum (D2)
- Proximal jejunum

Colonoscopy (n=15):

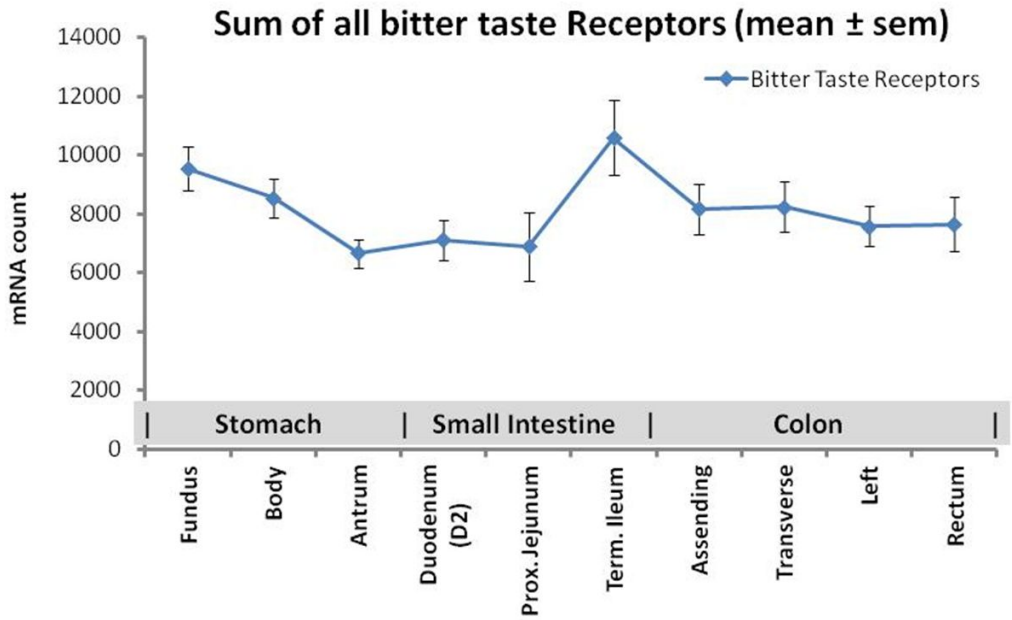
- Terminal Ileum
- Ascending
- Transverse
- Sigmoid colon
- Rectum



Gastrointestinal Bitter Taste Receptor Expression exhibits inter-regional, inter-individual and cytogenetic variation. Edward Walker, Russell Walmsley, Kate Richards, Ann-Thea McGill,, Sally D Poppitt , and John Ingram (Manuscript in prep)

Bitter Taste Receptors Gut Region

- Total of 30 procedures. 15 gastroscopy and 15 colonoscopy procedures
- 28 participants recruited. Two participants gave samples from both gastroscopy and colonoscopy procedures
- Bitter Taste Receptors are expressed throughout the gut. Elevated at the Gastric Fundus and Terminal Ileum



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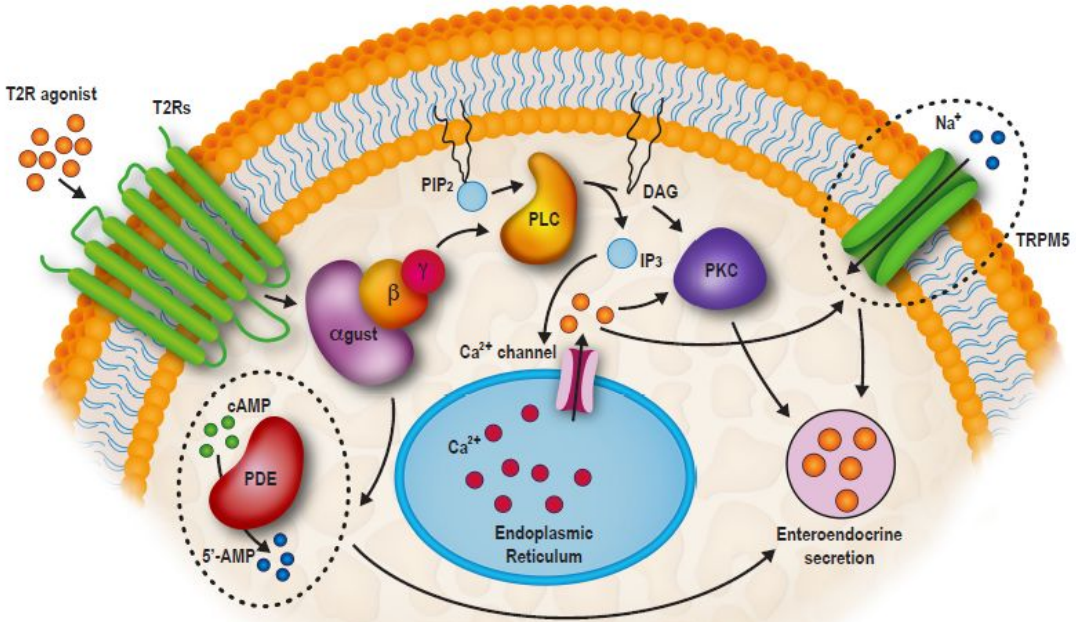
Can we Activate the Bitter Brake in the Lab?

Lab-Based Enteroendocrine cell assay

- High throughput robot assisted screening.
- Human gut enteroendocrine cells (CCK, GLP-1 producing)
- Bitter receptor (Tas2R) signaling measurable by Ca2+ changes.
- Tested over 1000 different plant extracts and compounds, as well as pharmaceuticals
- Hops identified as the clinical lead.



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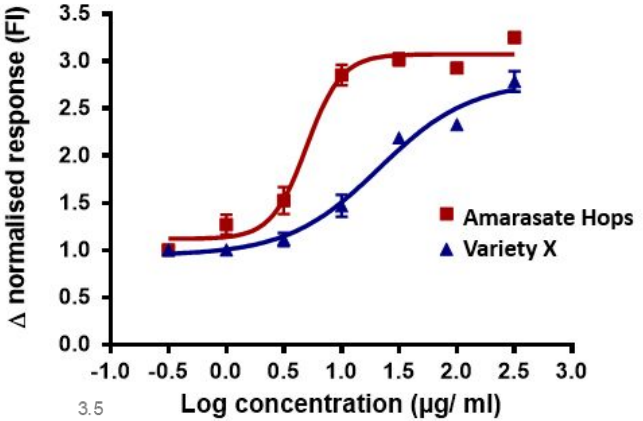
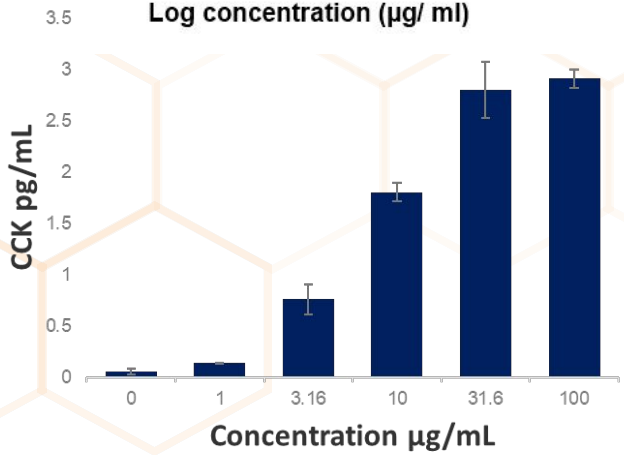
Amarasate®

(from Latin Amarum “bitter” and Satietas “satiety)

- Comparison of numerous hops cultivars identified Amarasate hop as the standout extract
- In-vitro enteroendocrine assay shows
  - Dose dependent increase in bitter receptor signaling
  - Dose dependent hormones release (CCK & GLP-1)





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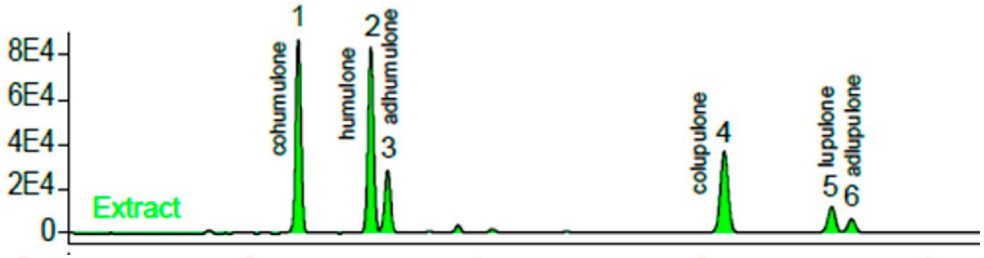
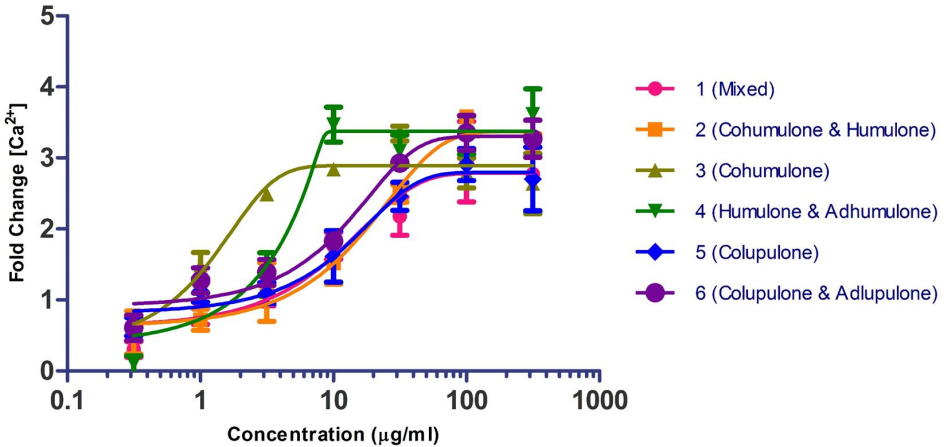
Bioactive Identification

- HPLC testing shows Amarasate extract contains:
  - Alpha acids - cohumulone, humulone, and adhumulone
  - Beta acids - colupulone, lupulone and adlupulone
- In-vitro enteroendocrine bioactivity shows
  - All components are bioactive
  - Cohumulone likely most potent bioactive
  - Cohumulone also most orally bitter





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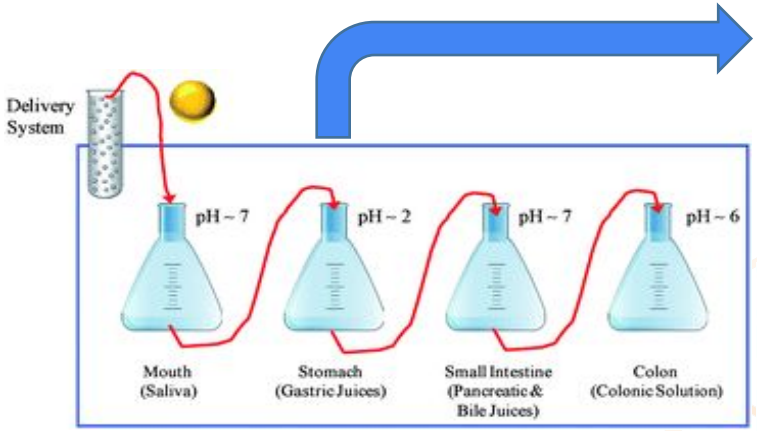
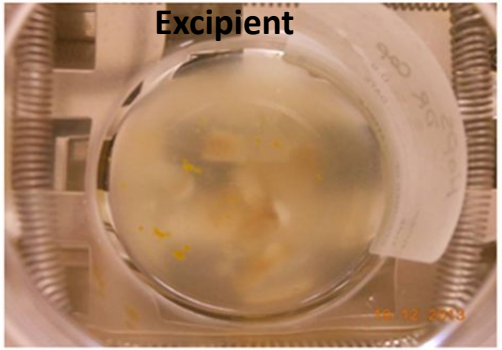
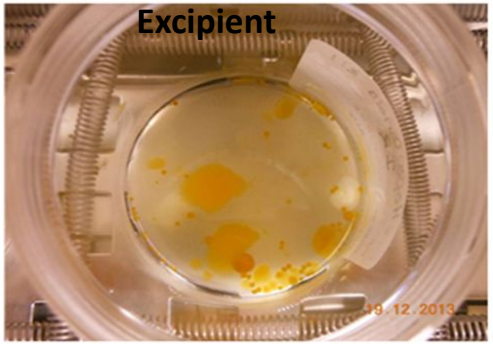
Testing Gut Dispersion of Hop Extract



No Excipient



With Excipient



McClements, D. J. and Y. Li (2010). "Review of in vitro digestion models for rapid screening of emulsion-based systems." Food & Function 1(1): 32-59. https://doi.org/10.1039/C0FO00111B

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Can we demonstrate clinical efficacy?

Bitter Brake Clinical Trial

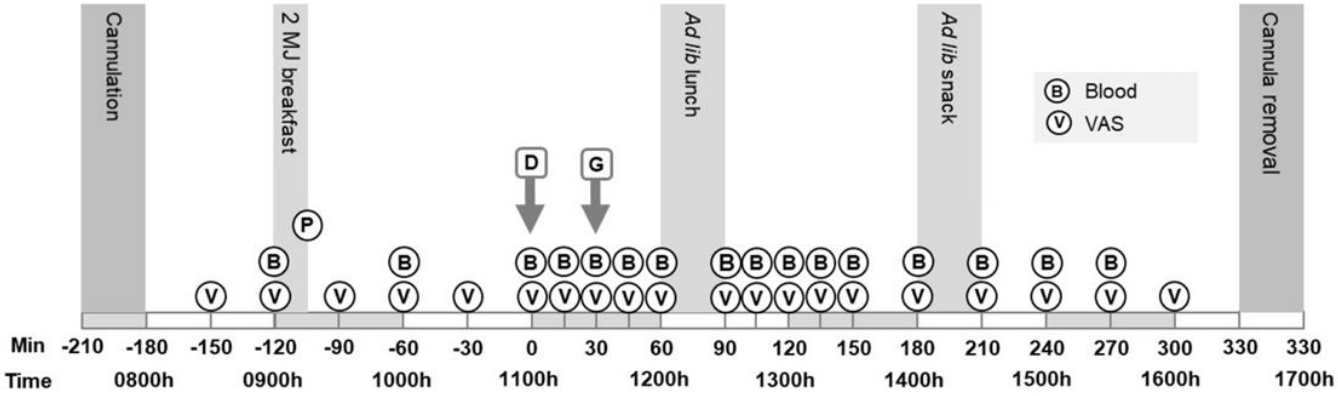
Design: Randomised, double blind, placebo controlled, cross over study in 20 men

Measurements

- Energy intake at *ad libitum* lunch and snack
- Appetite regulating peptide hormones.
- Subjective hunger and fullness by visual analogue scores (VAS)

Treatments:

- Gastric
- Duodenum
- Placebo Control



Edward G Walker, Kim R Lo, Malcolm C Pahl, Hyun Sang Shin, Claudia Lang, Mark W Wohlers, Sally D Poppitt, Kevin H Sutton, John R Ingram An extract of hops (Humulus lupulus L.) modulates gut peptide hormone secretion and reduces energy intake in healthy weight men: a randomised, cross-over clinical trial

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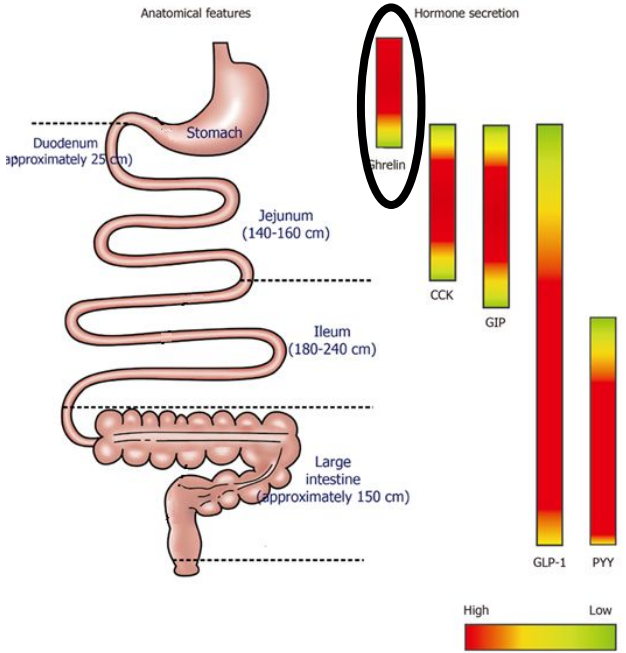
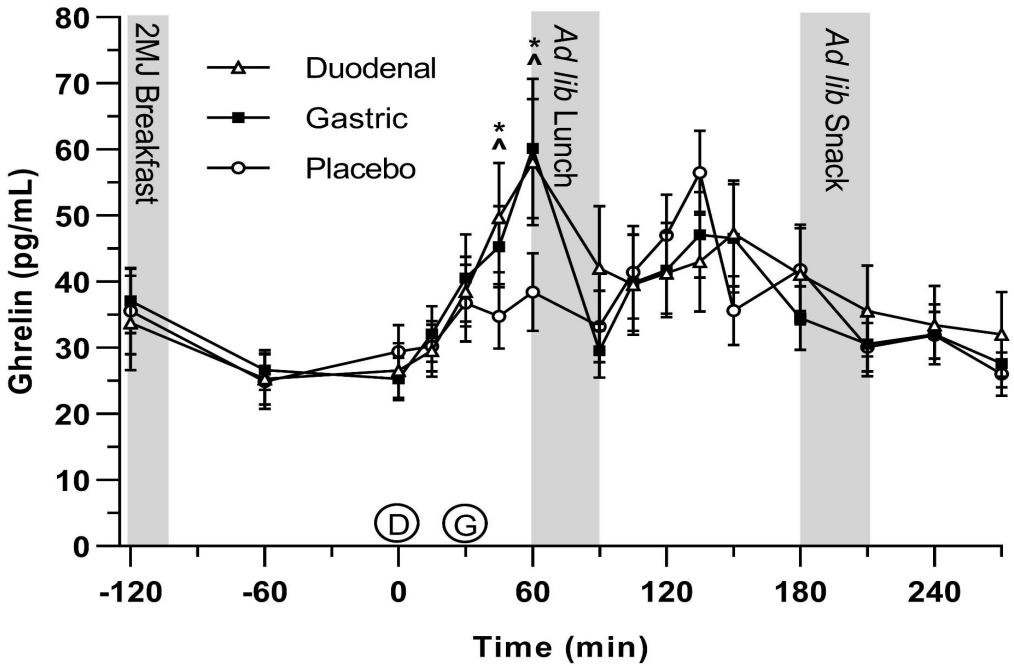
Ghrelin (Appetite Stimulating Hormone)





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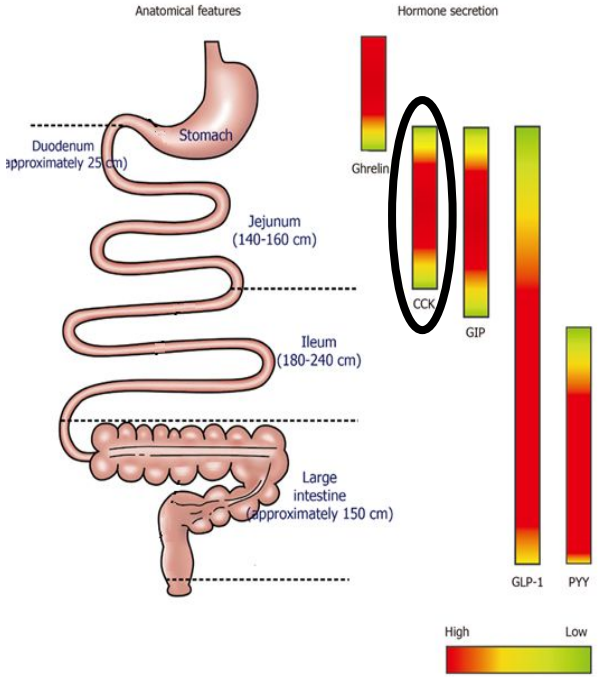
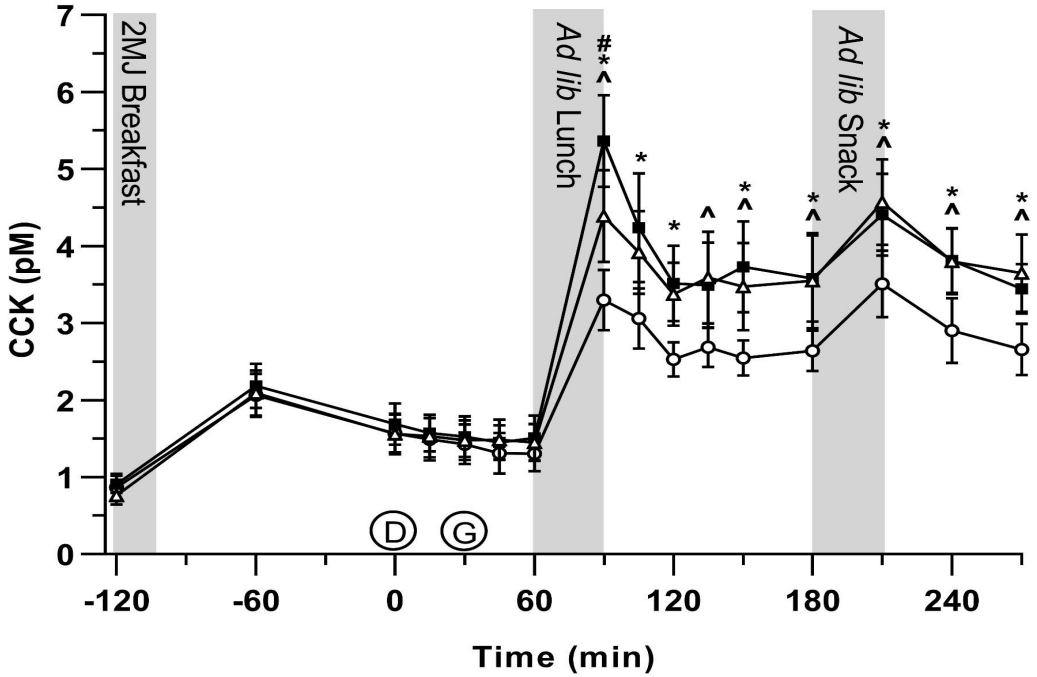
CCK (Appetite Suppressing Hormone)





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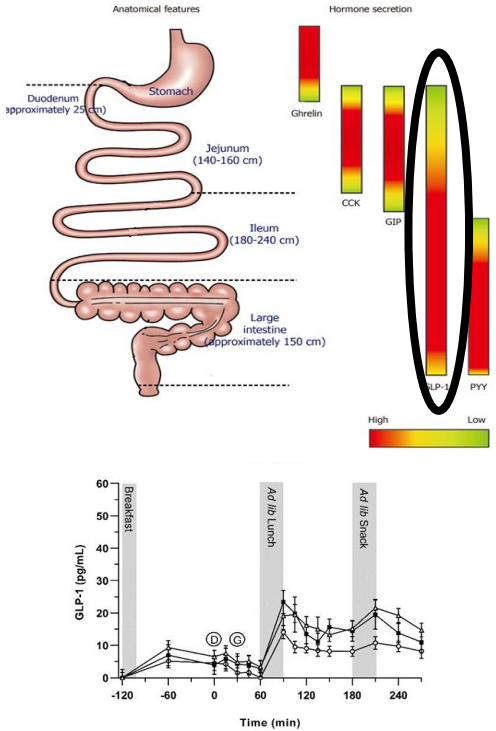
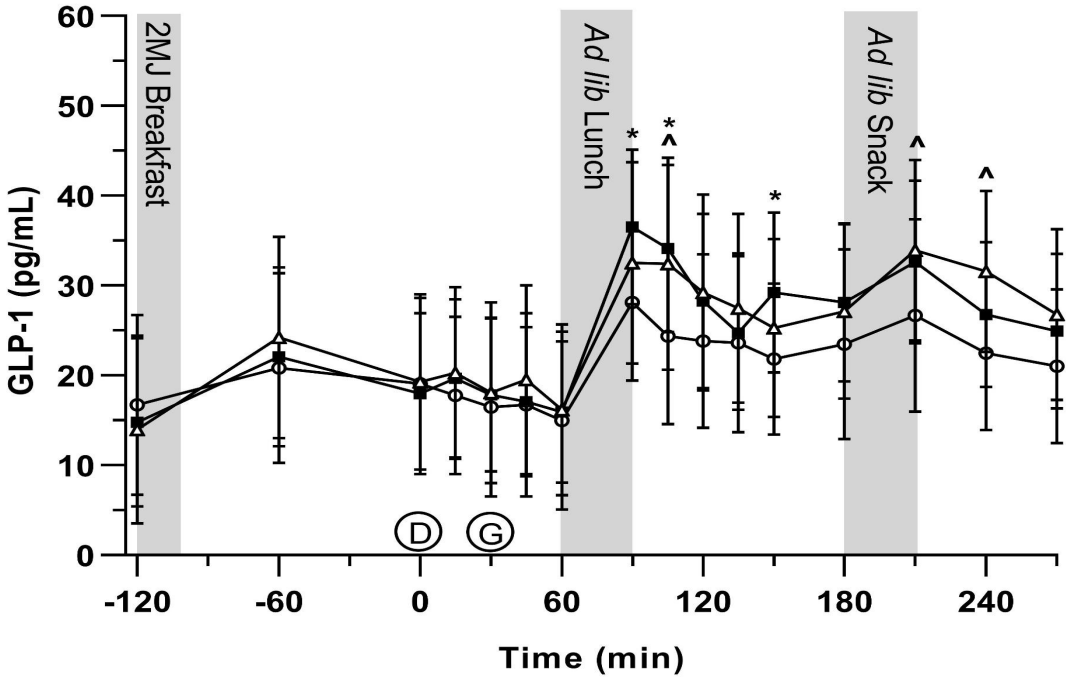
GLP-1 (Appetite Suppressing Hormone)





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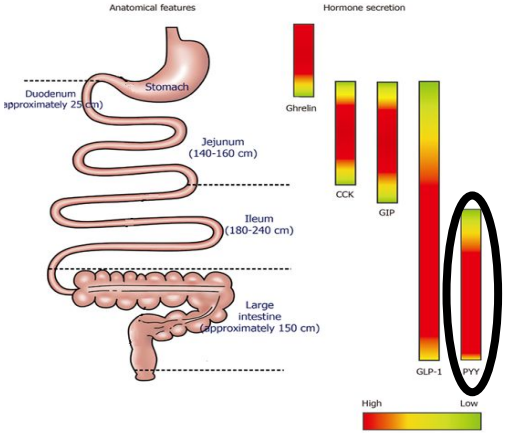
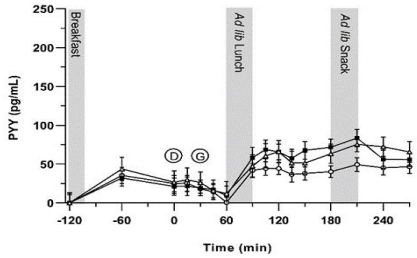
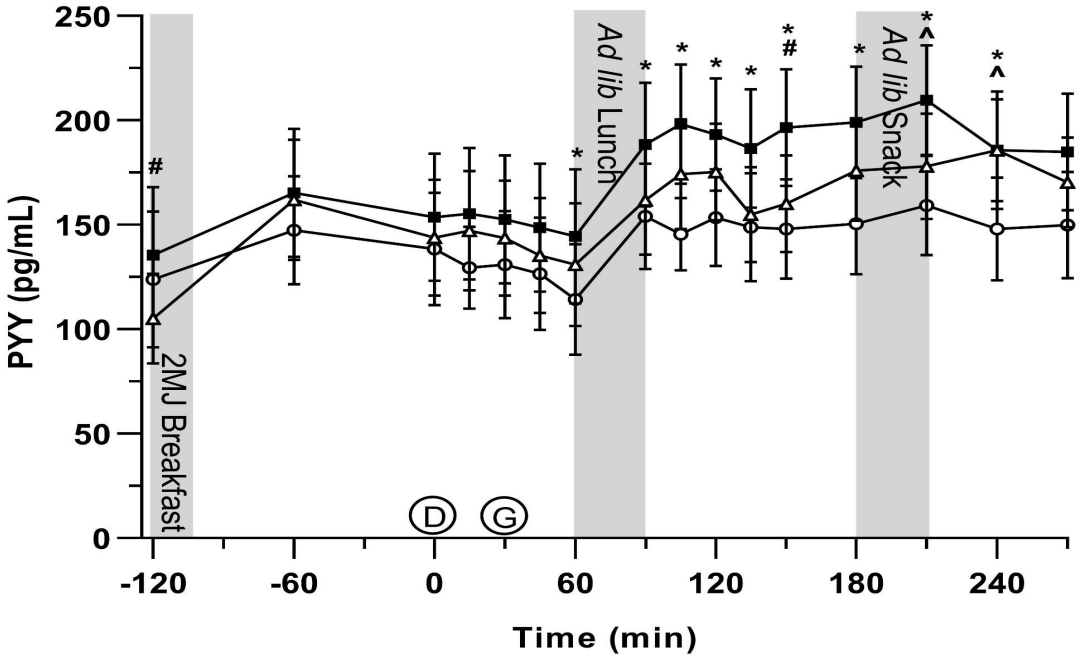
PYY (Appetite Suppressing Hormone)







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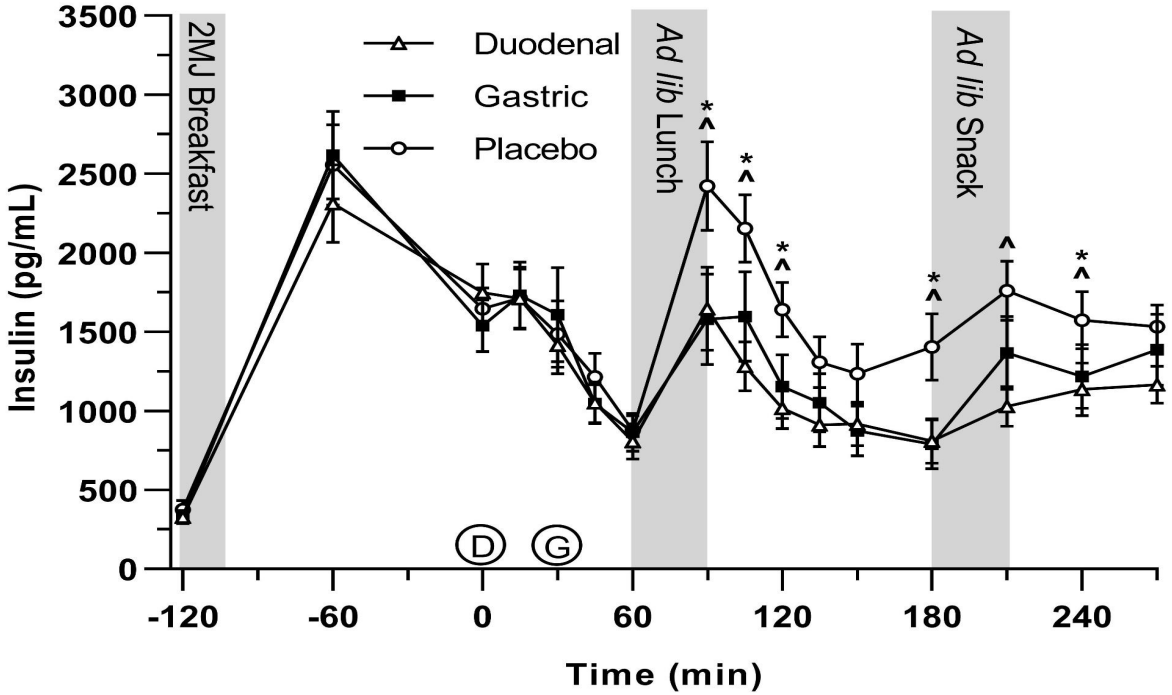
Insulin



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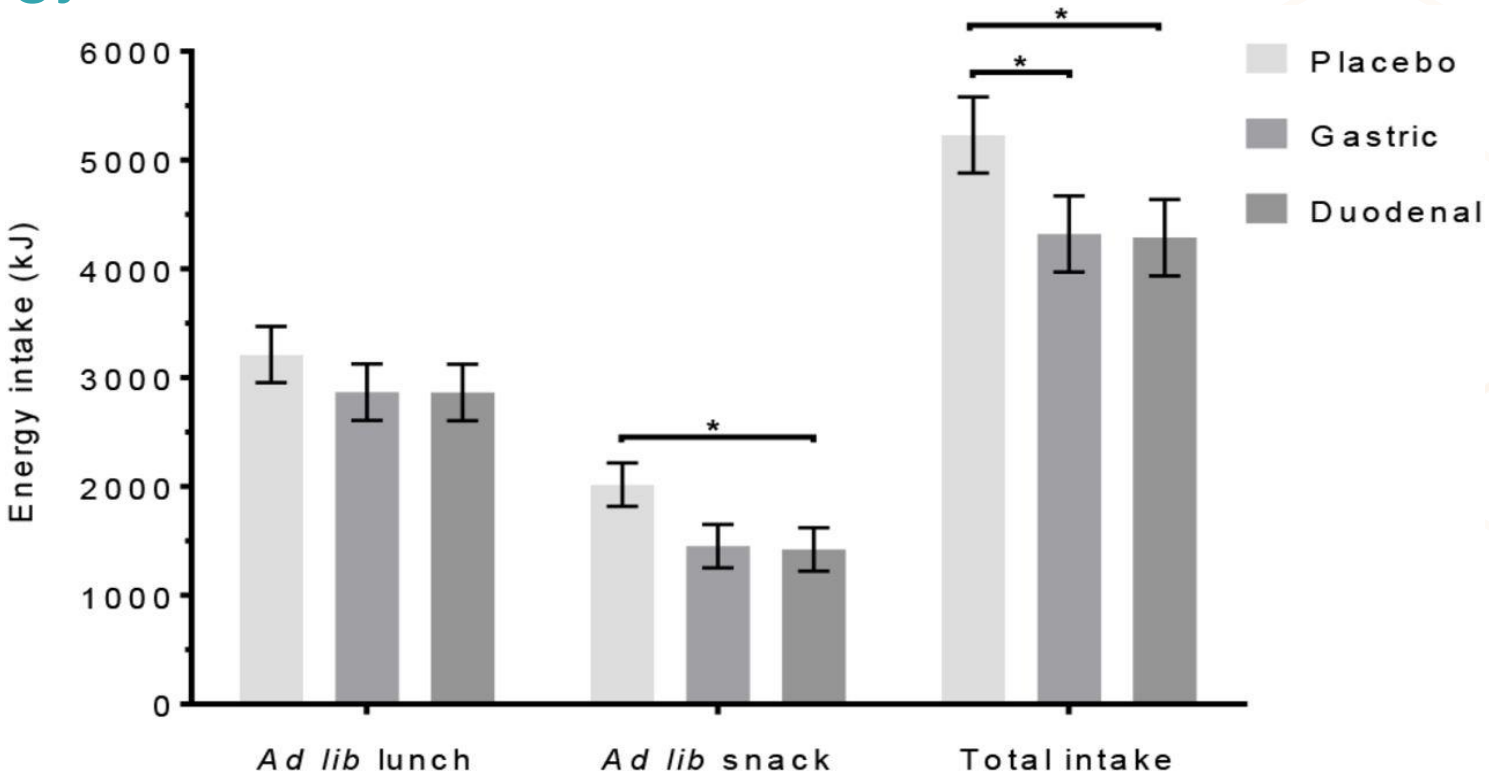
Energy Intake



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Use as part of a weight loss strategy

Acute 24h Water Only Fasting Study

Design: Randomised, double blind, placebo controlled, cross over study

Measurements

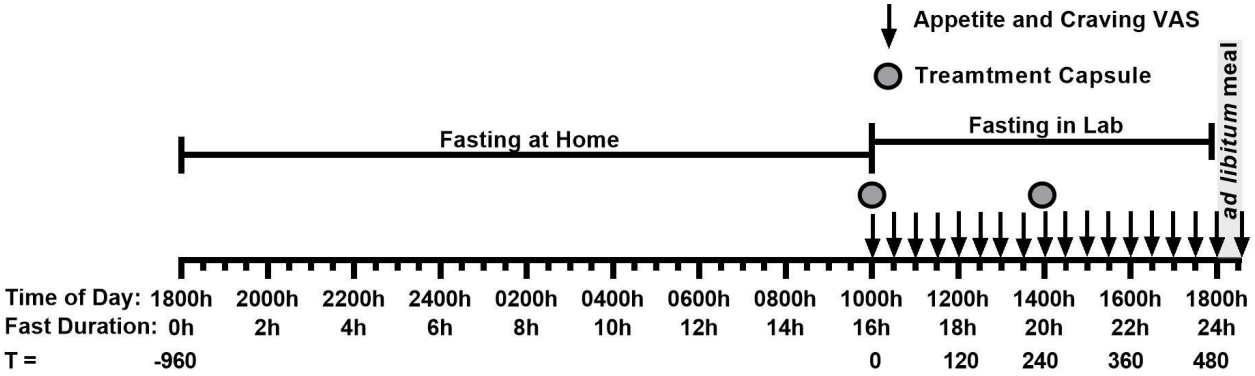
- Subjective hunger, fullness and food cravings (females only) by visual analogue scores (VAS)
- Energy intake at *ad libitum* fast braking meal (females only)

Treatments

- Low Dose 200mg Bitter Hops
- High Dose 500mg Bitter Hops
- Placebo Control

Participants

- Participants:
- Study 1: 30 males
- Study 2: 30 females (27 completed)



Walker E, Lo K, Tham S, Pahl M, Lomiwes D, Cooney J, Wohlers M, Gopal P. New Zealand Bitter Hops Extract Reduces Hunger During a 24 h Water Only Fast. Nutrients. 2019 Nov 13;11(11):2754. doi: 10.3390/nu11112754

Walker E, Lo K, Gopal P. Gastrointestinal Delivery of Bitter Hops Extract Reduces Appetite and Food Cravings in Healthy Adult Women Undergoing Acute Fasting (Manuscript submitted for publication).

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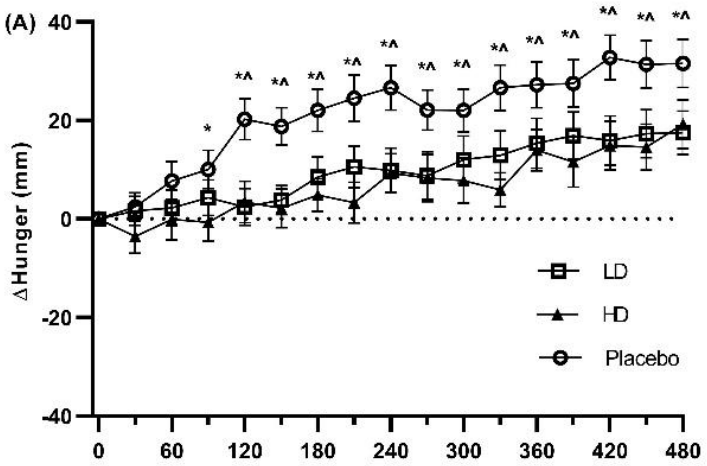
Hunger during 16-24h of fast

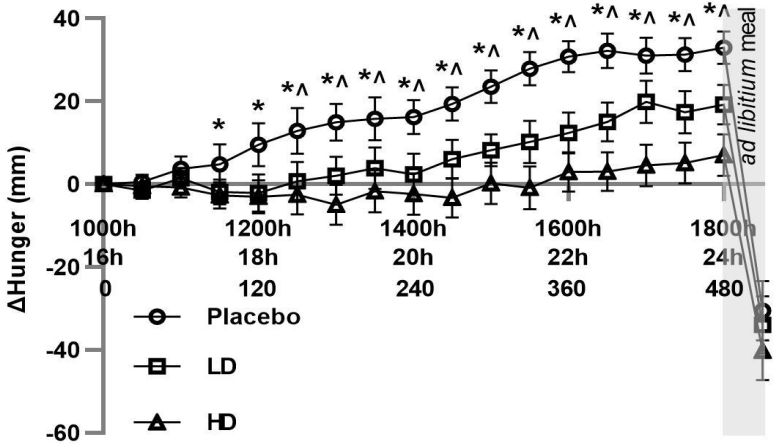
How hungry do you feel?

I am not hungry at all

I am as hungry as I've ever been



Males



Females

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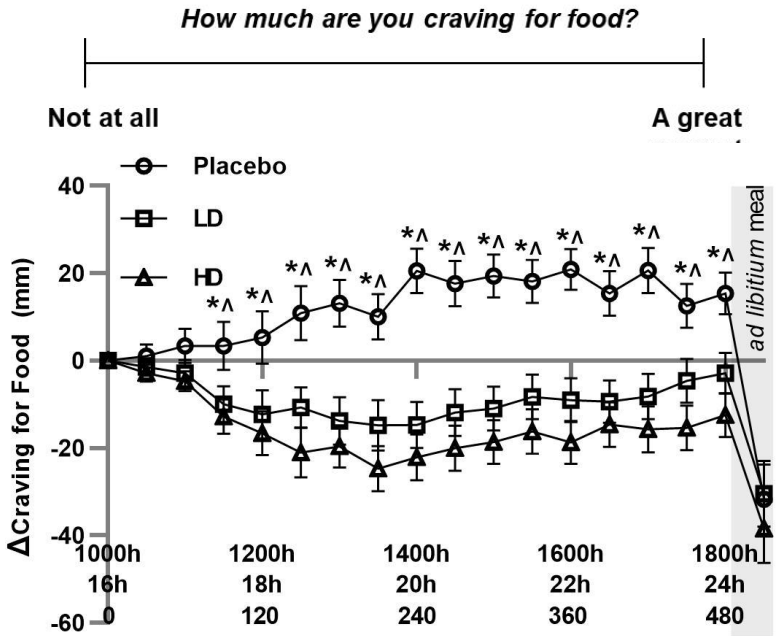
Craving for Food During 16-24h of Fast



Note: Energy intake at the ad libitum meal was 14.3% lower when taking the HD treatment ($p < 0.05$) and 8.1% lower when taking the LD treatment (not significant) relative to the placebo control treatment.

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Panel Discussion: Clinical Applications

Ovationlab.com/Calocurb
Resources and Free Bottle

https://www.ovationlab.com/calocurb

TAKE THE CALOCURB CHALLENGE

Suggested Use

The standard recommendation is to take one capsule daily for 2-3 days and build up to two capsules 1 hour prior to a meal. Up to four capsules can be taken per day

Dosing may be tailored depending on a patients requirements such as a specific diet or hunger times. Up to 4 capsules can be taken to reach the recommended dose.

Statements & Warnings

Due to the nature of the human clinical trials, results are based on adult dietary intake. This product is intended for adults only.

Calocurb should not be taken by individuals that have any form of gastrointestinal inflammation or inflammatory bowel disease, such as Crohn's or ulcerative colitis. Calocurb is not indicated for patients with type 1 diabetes mellitus.

Calocurb has also not been tested in pregnant or lactating women. In the absence of sufficient data, the use is not recommended. Calocurb is metabolized in the large intestine within 24 hours and a seminal study shows non-alcoholic beer residues in breast tissue and serum were negligible (Bolca et al., 2010). If a female patient wishes to get pregnant, she can discontinue the use of Calocurb, and it will

FREQUENTLY ASKED QUESTIONS

- **Who developed the active ingredient, Amarasate® in Calocurb?**
  - Amarasate®, the active ingredient in Calocurb was developed in NZ by a group of Scientists at the largest NZ government-owned research institute, Plant and Food Research (www.plantandfood.com) over 13 years and $25m invested. Over 900 plant extracts were tested using an in-vitro enteroendocrine cell model. The most potent extract (Amarasate®) was then taken into clinical human trials.

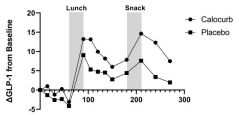
- **How does Calocurb compare to the latest anti-obesity medications in terms of its Mechanism of Action?**
  - Amarasate ® stimulates the body's own release of GLP-1 and CCK to 6 times baseline levels within an hour, lasting up to 4 hours. If Calocurb is taken one hour before a meal, the natural response to eating a meal will follow, with an enhanced appetite suppression that is slightly prolonged but gradually tapers off. This allows individuals to achieve a harmonious balance between their gut and brain appetite functions. Semaglutide injectables increase synthetic levels of GLP-1 agonists at supra-physiological concentrations, resulting in long-lasting effects due to their resistance to breakdown and do not follow the natural rhythm of hormone release.

- **Has a weight-loss study been conducted using Calocurb?**
  - A six-month weight loss study with a three-month follow-up period is planned to begin in 2023 to assess the long-term effectiveness of Calocurb as a weight loss supplement. This study is designed as a randomized, double-blind, crossover clinical trial in 150 adult men and women with a BMI > 30.
    It is worth noting that the GLP-1 system, which is targeted by Calocurb, has shown effectiveness for weight management.

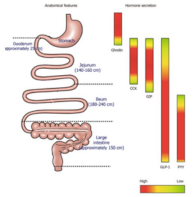
Research Highlights

Clinical 1: Amarasate® mode of action

- Randomised 3 treatment, double-blind, crossover study in adult healthy men
- Calocurb was given an hour before an ad libitum lunch (including a snack)
- Blood samples and caloric intake were measured over 4 hours

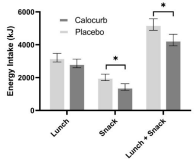


- CCK/GLP-1 were increased 6x above baseline and twice the normal post-prandial release of gastric hormones over 4 hours following the body's endogenous hormonal release cycle



- Amarasate ® passes down the intestinal tract stimulating the gastrointestinal bitter taste receptors (TAS2R) to release appetite suppressing hormones GLP-1, CCK and PYY in specific sections of the digestive tract. Over 99% of Amarasate ® is then degraded on the large intestine.

- With an average of 18% reduction in calorie intake



Walker, E. et al (2022). An extract of hops (Humulus lupulus L.) modulates gut peptide hormone secretion and reduces energy intake in healthy-weight men: a randomized, crossover clinical trial. The American Journal of Clinical Nutrition, 115(3), 925–940.

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