

**Nature's Catalysts:
exploring the impact of
herbs and spices on
metabolism**

Professor Kerry Bone and Simon Mills

The prospects

Conditions such as diabetes, obesity and cardiovascular disease are associated with diet and lifestyle, therefore adjustments to eating patterns could be a crucial tool to tackle them especially if these were practicable, inexpensive and even enjoyable!

Herbs and spices have been found to modulate many of the risk factors for cardiometabolic disease including features associated with 'Metabolic Syndrome'. Many of these are particularly rich sources of bioactives such as polyphenols (including flavonoids) known to benefit cardiometabolic health.

Liu XM, Liu YJ, Huang Y, et al. (2017) Dietary total flavonoids intake and risk of mortality from all causes and cardiovascular disease in the general population: A systematic review and meta-analysis of cohort studies. *Mol Nutr Food Res*. PMID: 28054441

In addition to culinary herb and spice intake, research in herbal medicine has pointed to further benefits, for example in the emerging evidence of the effects of bitters. Most cultures have also incorporated these into everyday life.

The Pukka campaign

As part of a wider social advocacy campaign to support healthier diets, the tea company Pukka Herbs collaborated with academics at Kings College London in a scoping review.

This identified 142 human randomized-controlled trials on common herbs and spices, most involving culinary doses.



Our paper





nutrients



Review

A Scoping Review of the Clinical Evidence for the Health Benefits of Culinary Doses of Herbs and Spices for the Prevention and Treatment of Metabolic Syndrome

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PMID: 38068725

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Abstract: Metabolic syndrome (MetS) is a growing global health problem. Evidence suggests that diets rich in phytochemical-containing herbs and spices can contribute to reducing the risk of chronic diseases. This review assesses the scope of evidence supporting the use of herbs and spices in the diet

How could these work?



Four mechanisms by which herbs and spices could improve cardiometabolic health emerged most clearly from this review:

the regulation of

- glycaemic control and blood glucose levels
- insulin resistance
- lipid metabolism
- obesity-related inflammation

Mackonochie M, Rodriguez-Mateos A, Mills S, Rolfe V. (2023) A Scoping Review of the Clinical Evidence for the Health Benefits of Culinary Doses of Herbs and Spices for the Prevention and Treatment of Metabolic Syndrome. *Nutrients*. PMID: 38068725

How could these work?

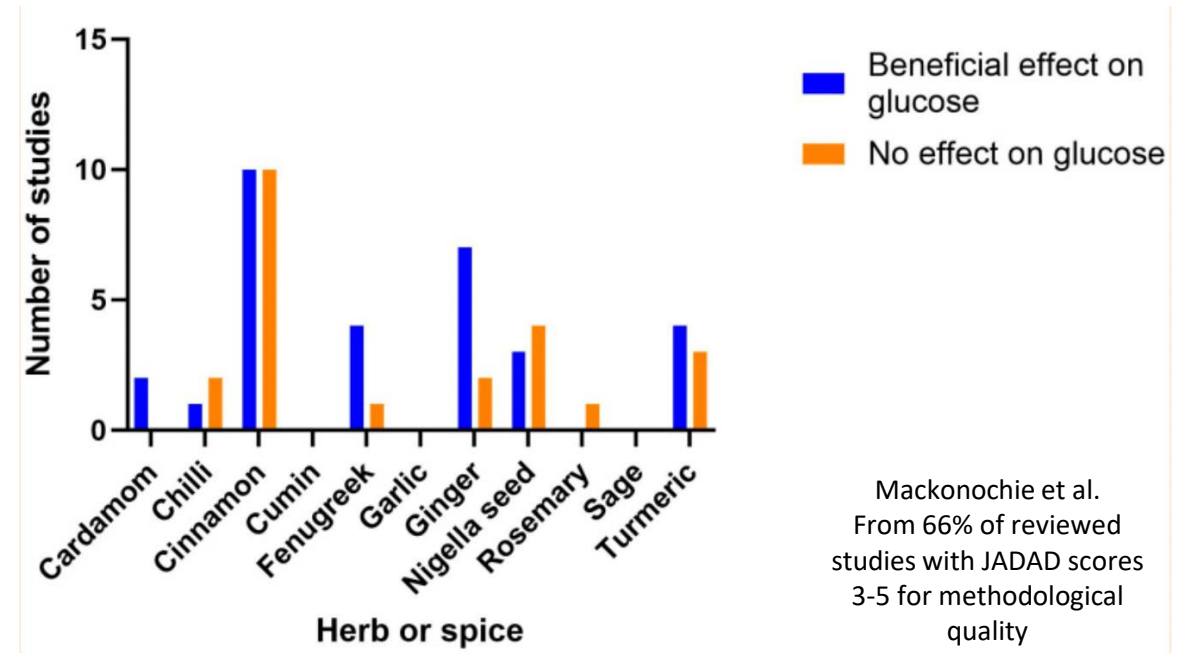


Glycaemic control and blood glucose levels

Cinnamon has long been associated with benefits on **blood glucose** regulation. However the evidence here is mixed, being stronger for ginger, fenugreek and turmeric.



A more recent systematic review concluded that that in Type 2 diabetic subjects, nigella, cinnamon and ginger were particularly effective in improving fasting glucose levels.



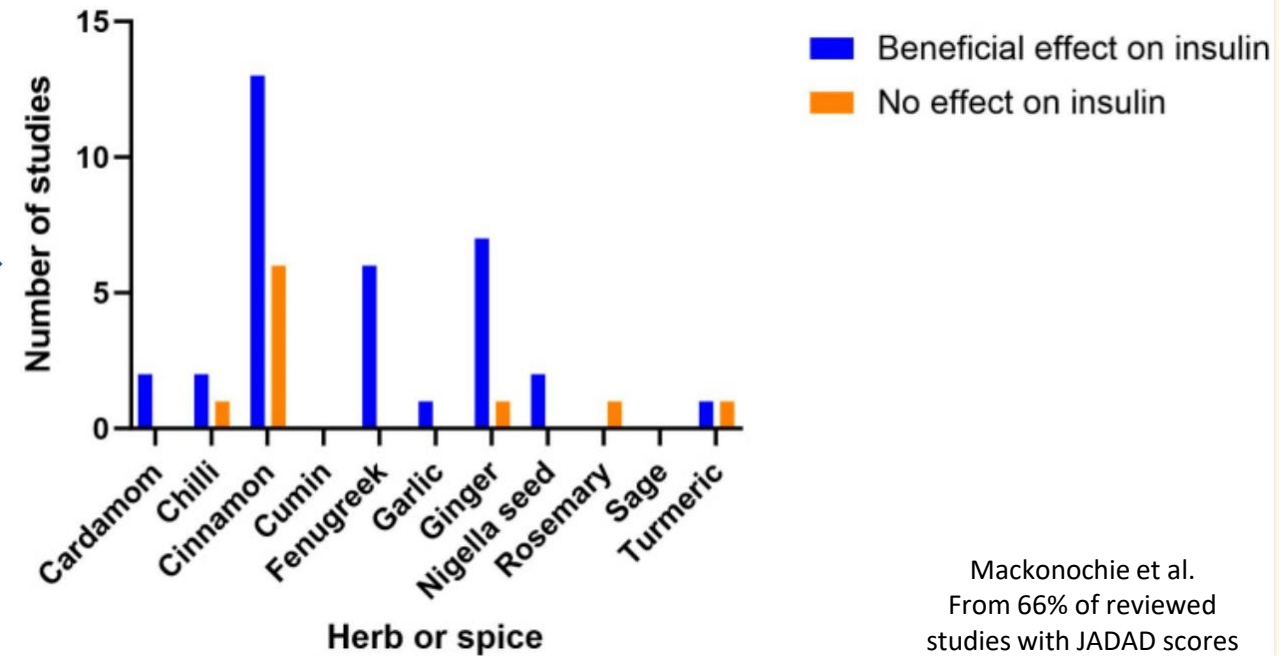
Garza MC, Pérez-Calahorra S, Rodrigo-Carbó C, et al. (2024) Effect of Aromatic Herbs and Spices Present in the Mediterranean Diet on the Glycemic Profile in Type 2 Diabetes Subjects: A Systematic Review and Meta-Analysis. *Nutrients*. 2024 PMID: 38542668

How could these work?

Reducing insulin resistance

Cinnamon performed better for reducing **insulin resistance**, again with fenugreek and ginger also promising. →

One cause is dysregulation of protein tyrosine phosphatase 1B (PTP1B) which is a new pharmaceutical target though so far generating undue adverse effects. Several herb and spice ingredients have been shown to regulate PTP1B.



Mackonochie et al.
From 66% of reviewed studies with JADAD scores 3-5 for methodological quality

Rath P, Ranjan A, Chauhan A, et al. (2022) A Critical Review on Role of Available Synthetic Drugs and Phytochemicals in Insulin Resistance Treatment by Targeting PTP1B. *Appl Biochem Biotechnol*. PMID: 35819691

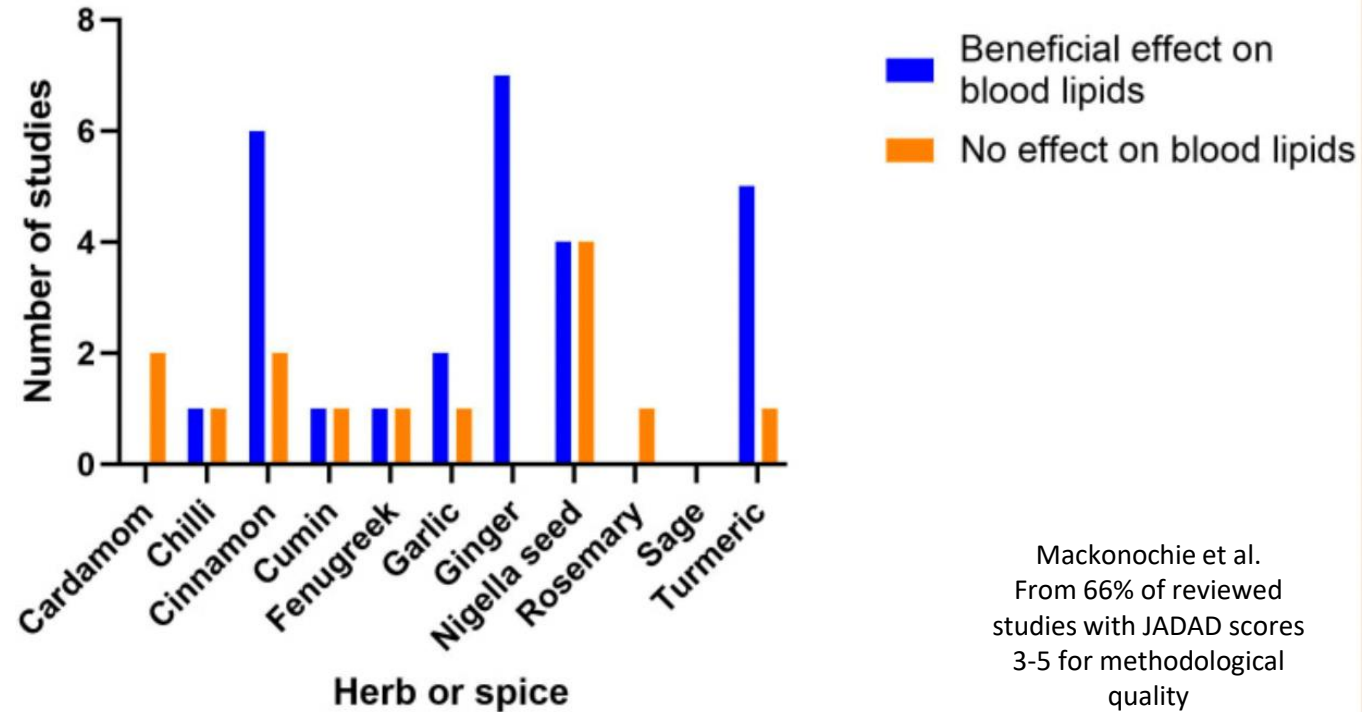
How could these work?

Lipid metabolism

Ginger, turmeric and cinnamon stand out as most promising leads so far for regulating **lipid metabolism**.



Bioactive compounds from spices may reduce lipid accumulation in fat cells and adipose tissues by regulating expression of transcriptional factors, by modulating lipogenesis and by thermogenesis.



Mackonochie et al.
From 66% of reviewed studies with JADAD scores 3-5 for methodological quality

Lu M , Cao Y , Xiao J , Song M , Ho CT . (2018) Molecular mechanisms of the anti-obesity effect of bioactive ingredients in common spices: a review. *Food Funct.*.. PMID: 30168574

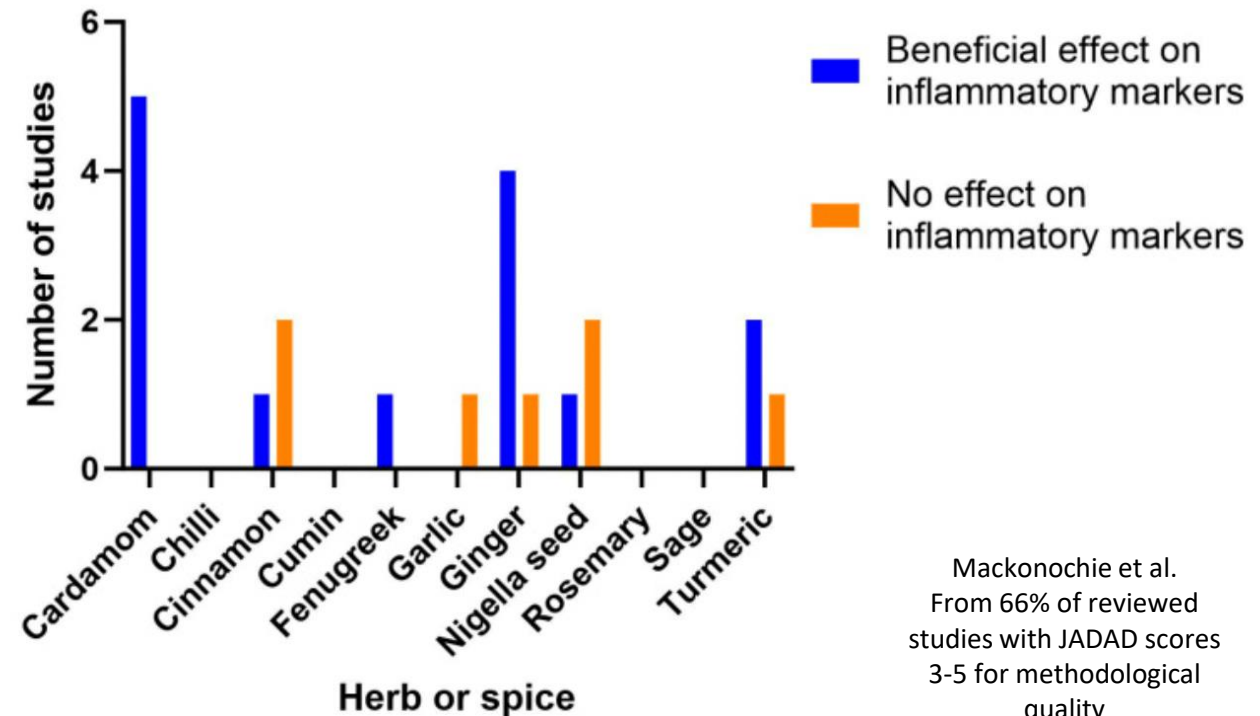
How could these work?

Obesity-related inflammation

Cardamon emerges with its relatives ginger and turmeric as best leads in reducing **inflammatory markers**.



There is clinical and epidemiological evidence for spice consumption to show how this effect could moderate obesity, insulin resistance and other metabolic problems.



Mackonochie et al.
From 66% of reviewed studies with JADAD scores 3-5 for methodological quality

Kunnumakkara AB, Sailo BL, Banik K, et al. (2018) Chronic diseases, inflammation, and spices: how are they linked? *J Transl Med*. PMID: 29370858

Jungbauer A, Medjakovic S. (2012) Anti-inflammatory properties of culinary herbs and spices that ameliorate the effects of metabolic syndrome. *Maturitas*. PMID: 22226987

The Evidence Leaderboard



	Range of metabolic benefits	Evidence rating so far
Ginger	Improved blood sugar and lipid control especially in diabetics, improved <u>digestion</u> and inflammatory markers; prebiotic	★★★★☆
Nigella (black seed)	Improved blood sugar and lipid control especially in diabetics, NAFLD (MASLD) and post menopause	★★★★☆
Fenugreek	Improved blood sugar control and lipid control especially in diabetics	★★★★☆
Cinnamon	Improved postprandial blood sugar control	★★★★☆
Turmeric	Improved blood lipid and sugar control; reduced inflammatory factors in metabolic disorders; prebiotic	★★★★☆
Cardamom	Improved blood sugar and lipid control including in diabetes, obesity and PCOS; reduced inflammatory factors in metabolic disorders	★★★☆☆
Chilli	Improved satiety and postprandial blood sugar control; prebiotic	★★★☆☆
Cumin	Improved blood sugar control and lipid control especially when overweight	★★★☆☆
Garlic	Improved metabolic markers in metabolic syndrome and NAFLD (MASLD); prebiotic	★★★☆☆
Rosemary	Improved blood sugar and lipid control	★★★☆☆
Sage	Improved lipid and sugar control	★★★☆☆

How could these work?

Other putative mechanisms by which plants like herbs and spices could manage metabolic problems have also been identified:

- the regulation of the gut microbiota
- thermogenesis and energy expenditure.

Shang A, Gan RY, Xu XY, et al. (2021) Effects and mechanisms of edible and medicinal plants on obesity: an updated review. *Crit Rev Food Sci Nutr*. PMID: 32462901x

Arif Icer M, Acar Tek N. (2023) Effects of Red Pepper, Ginger, and Turmeric on Energy Metabolism: Review of Current Knowledge. *Altern Ther Health Med*. PMID: 33789250

Westerterp-Plantenga M, Diepvens K, Joosen AM, et al. (2006) Metabolic effects of spices, teas, and caffeine. *Physiol Behav*. PMID: 16580033

How could these work?

Prebiotic and **postbiotic** effects of herbs and spices in positively modulating the gut microbiome are increasingly evident.¹ There are reasons to propose that these properties may also reduce metabolic disturbances.

Identified mechanisms so far include

- shifts in microbiota populations away from inflammatory organisms (eg by ginger² and turmeric³).
- secretion of GLP-1⁴ and modulation of TLR-4⁵ signals by curcumin metabolites.

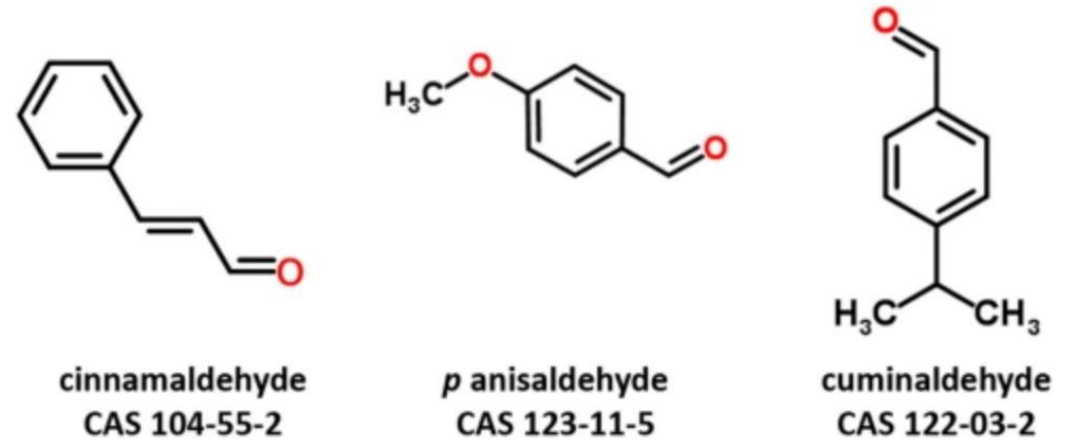
1. Mills S (2022) Plants and the Gut Microbiome: Prebiotics and Postbiotics. *Herbal Reality* <https://tinyurl.com/48y8s62p>
2. Wang X, Zhang D, Jiang H, et al. (2021) Gut Microbiota Variation With Short-Term Intake of Ginger Juice on Human Health. *Front Microbiol.* PMID: 33708178
3. Zam W. (2018) Gut Microbiota as a Prospective Therapeutic Target for Curcumin: A Review of Mutual Influence. *J Nutr Metab.* PMID: 30647970
4. Alli-Oluwafuyi AM, Luis PB, Nakashima F, et al. (2019) Curcumin induces secretion of glucagon-like peptide-1 through an oxidation-dependent mechanism. *Biochimie.* PMID: 31470039
5. Panaro MA, Corrado A, Benameur T, et al. (2020) The Emerging Role of Curcumin in the Modulation of TLR-4 Signaling Pathway: Focus on Neuroprotective and Anti-Rheumatic Properties. *Int J Mol Sci.* PMID: 32225104

How could these work?

There is a new intriguing mechanism.

The transient receptor potential ankyrin 1 (**TRPA1**) channel, initially studied for its role in pain and inflammation, has now been associated with the regulation of hunger and satiety hormones, insulin secretion and thermogenesis, and has become a target for weight reduction and associated comorbidities.

Some pungent compounds in spices and herbs plants have demonstrated TRPA1 agonist properties.



Chemical structures of natural TRPA1 agonists

Legrand C, Merlini JM, de Senarclens-Bezençon C, Michlig S. (2020) New natural agonists of the transient receptor potential Ankyrin 1 (TRPA1) channel. *Sci Rep*. PMID: 32641724

Mahajan N, Khare P, Kondepudi KK, Bishnoi M. (2021) TRPA1: Pharmacology, natural activators and role in obesity prevention. *Eur J Pharmacol*. PMID: 34627805

There could be other promising leads ...

Welcome to the word of **bitters**



with Professor Kerry Bone!

- Impact of GLP-1 analogues (that act as incretin mimetics) to effect weight loss and restore metabolic balance has been extraordinary
- As injectable drugs they help the body produce more insulin (only when needed) and reduce the amount of glucose produced by the liver
- They reduce the rate at which the stomach digests food and empties, and also markedly reduce appetite

Semaglutide is causing a social media frenzy. So what is it?

By Judd Boaz

Posted Sat 17 Dec 2022 at 5:15am, updated Sat 17 Dec 2022 at 11:51 pm



An injector pen is used to administer semaglutide. (Getty Images)

The latest craze on social media is not a dance challenge or a viral meme, but an injectable medication originally designed to treat diabetes.

Known as semaglutide and marketed under names such as Ozempic and Wegovy, the drug has recently gained popularity as a weight-loss tool.

TikTok and Instagram videos theorise Kim Kardashian used the medication to lose weight for her outfit at the 2022 Met Gala.

Celebrity doctor and republican candidate Dr Oz spruiked semaglutide on his television show, and billionaire Elon Musk tweeted that the drug featured in his own weight-loss regime.



Weight loss pills aren't a replacement for a healthy diet and lifestyle. JW LTD/Stone via Getty Images

Your body already has a built-in weight loss system that works like Wegovy, Ozempic and Mounjaro – food and your gut microbiome

Published: January 17, 2024 12.40am AEDT

Christopher Damman

Associate Professor of Gastroenterology, School of Medicine, University of Washington

Wegovy, Ozempic and Mounjaro are weight loss and diabetes drugs that have made quite a splash in health news. They target regulatory pathways involved in both obesity and diabetes and are widely considered breakthroughs for weight loss and blood sugar control.

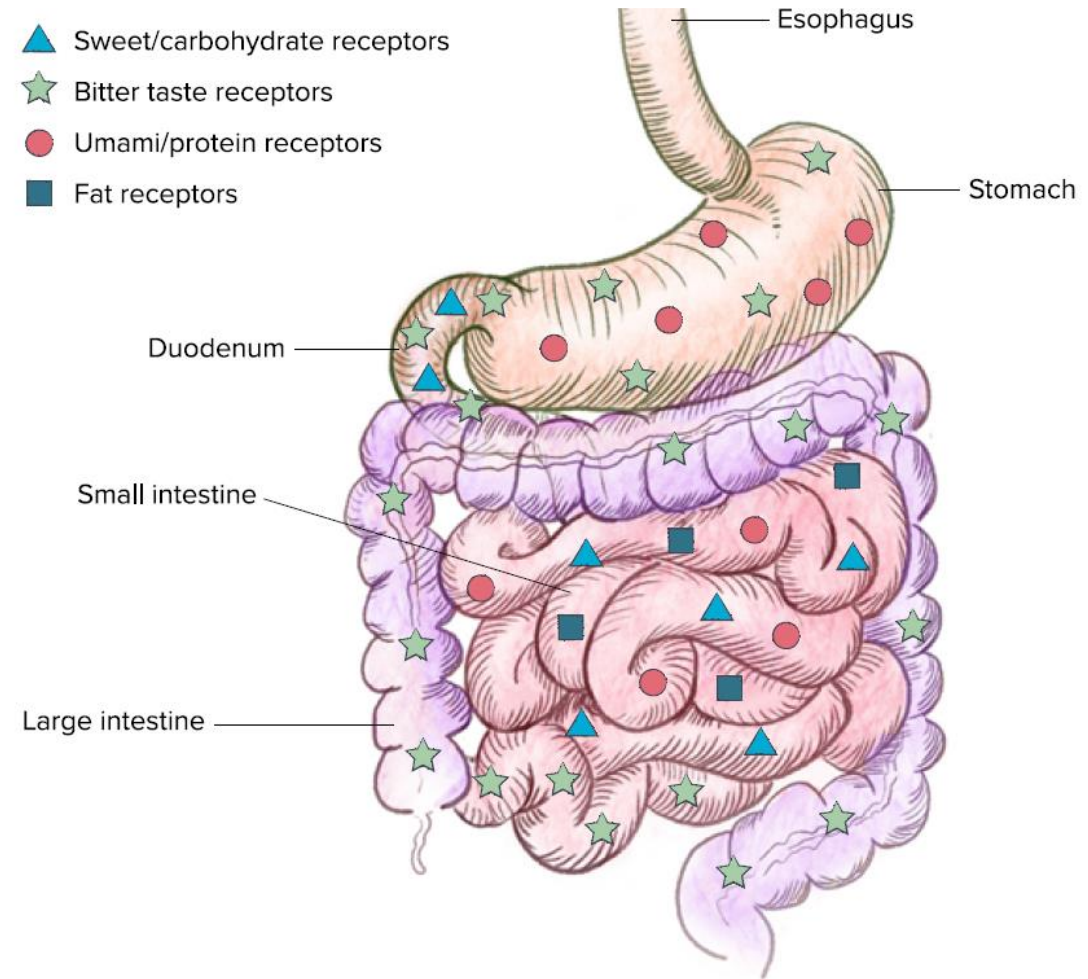
But do these drugs point toward a root cause of metabolic disease? What inspired their development in the first place?

It turns out your body produces natural versions of these drugs – also known as incretin hormones – in your gut. It may not be surprising that nutrients in food help regulate these hormones. But it may intrigue you to know that the trillions of microbes in your gut are key for orchestrating this process.

...and bitter receptors

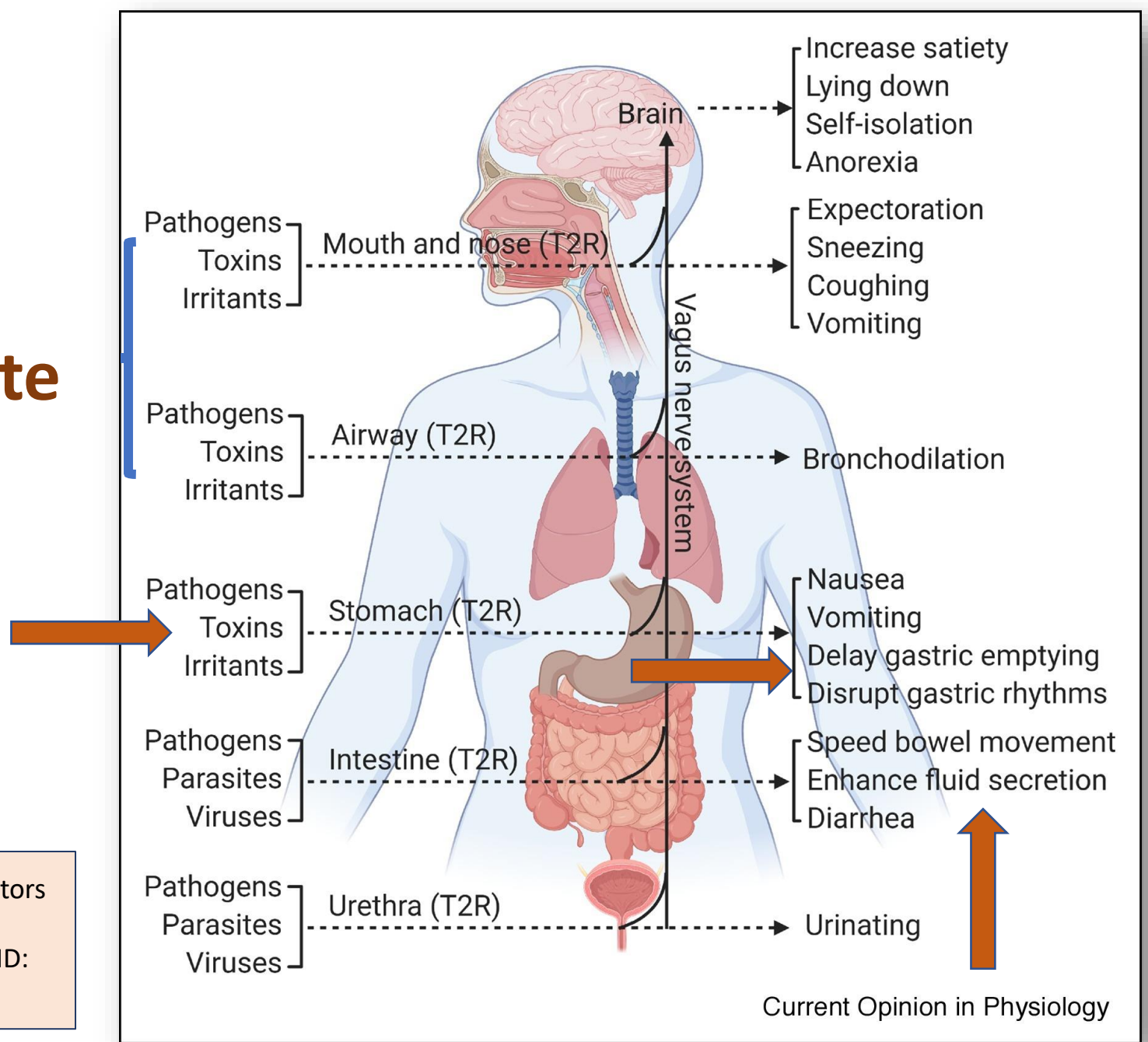
Bitter Receptors Explode!

- Up until the early 2000's \Rightarrow bitter receptors only on the tongue
- Since then found throughout the digestive tract and elsewhere
- Main extra-oral cell in gut bearing bitter receptors \Rightarrow enteroendocrine cell, but also Tuft cells

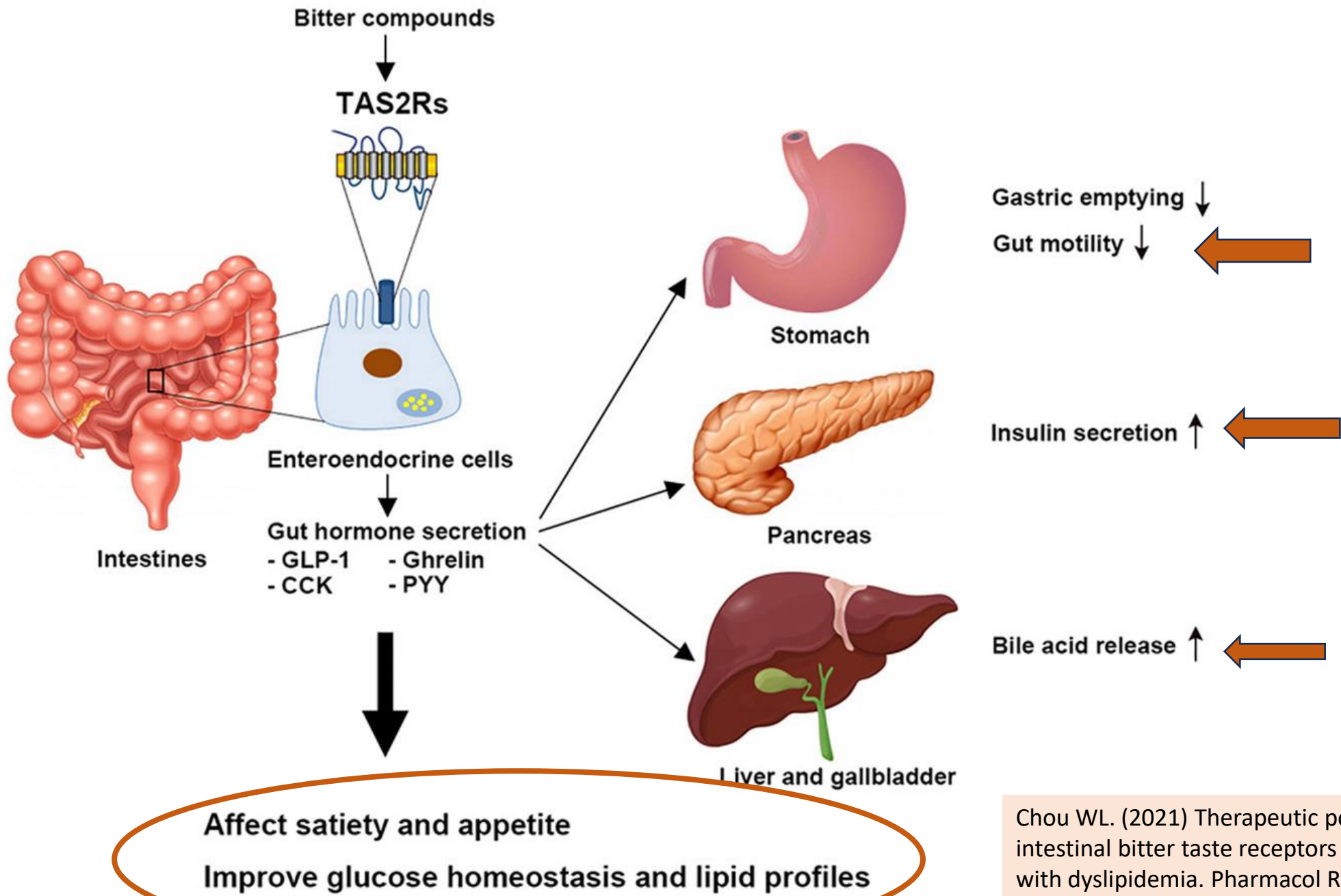


Bitter Receptors: Sentinels that Coordinate Metabolic and Immune Responses

Harmon CP, Deng D, Breslin PAS. (2021) Bitter Taste Receptors (T2Rs) are Sentinels that Coordinate Metabolic and Immunological Defense Responses. *Curr Opin Physiol*. PMID: 33738371



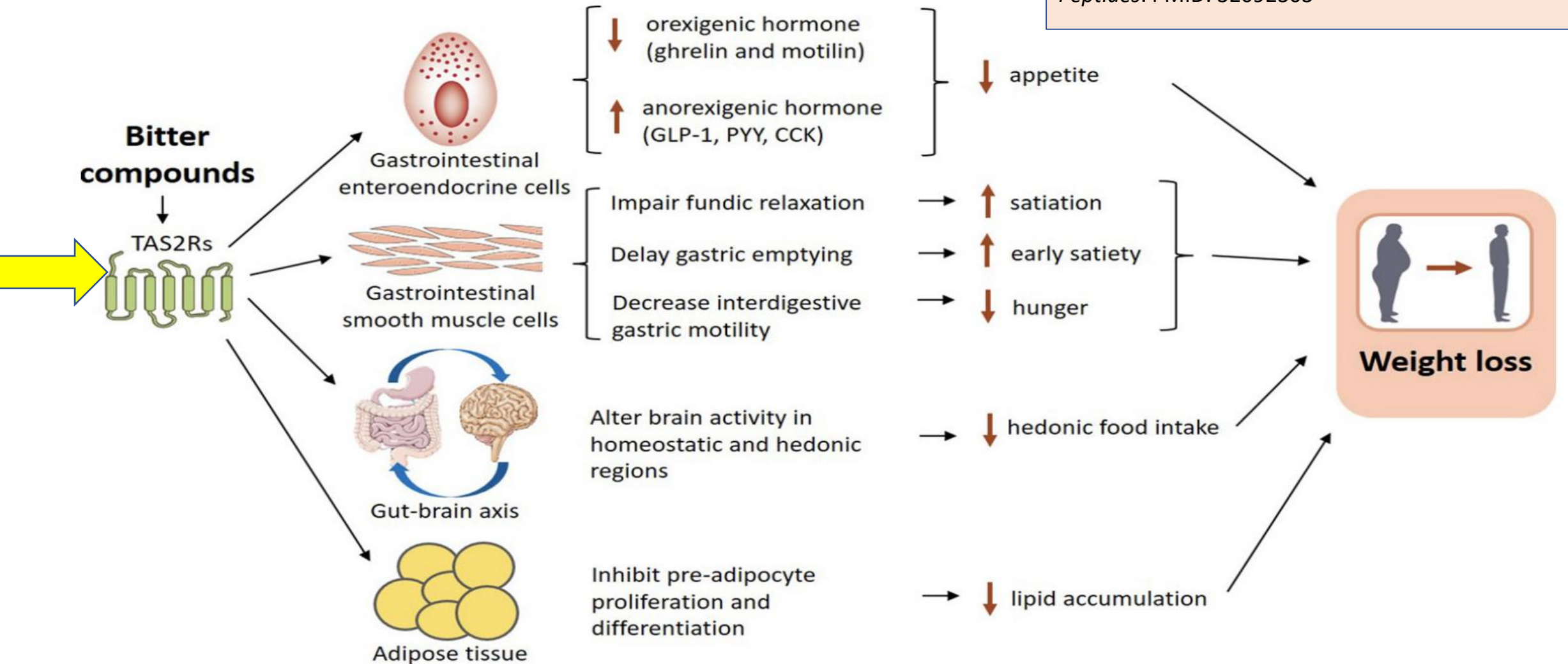
Current Opinion in Physiology

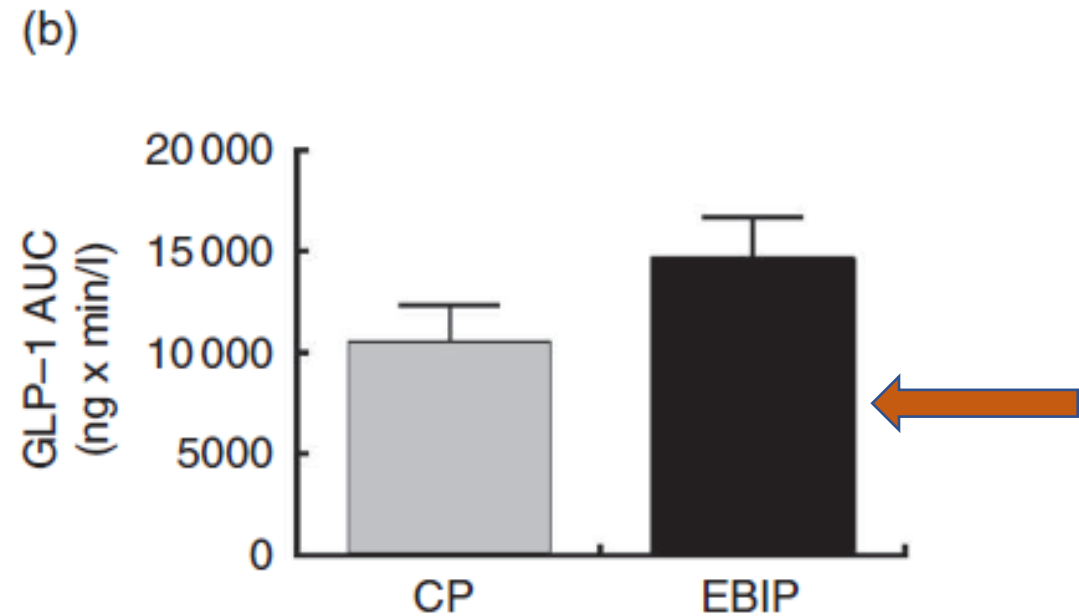
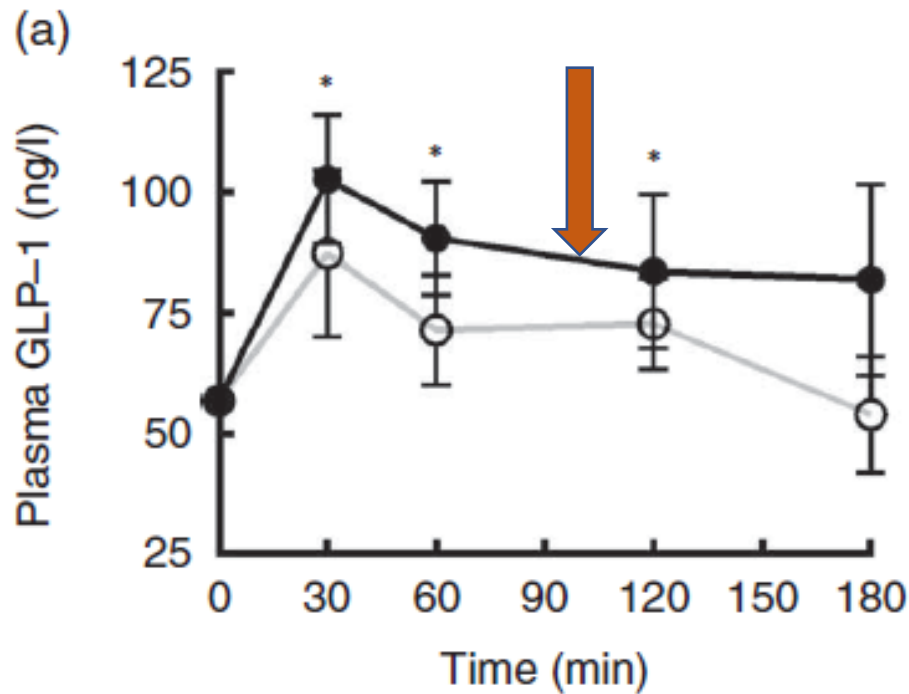


Chou WL. (2021) Therapeutic potential of targeting intestinal bitter taste receptors in diabetes associated with dyslipidemia. Pharmacol Res. PMID: 34048925

Bitters and Weight Loss

Wang Q, Liszt KI, Depoortere I. (2020) Extra-oral bitter taste receptors: New targets against obesity? *Peptides*. PMID: 32092303





A cross-over randomised study was performed: twenty healthy people consumed at breakfast EBIP (microencapsulated gentian-enriched pudding providing 100mg of secoiridoids) or a control pudding (CP) on two different occasions

Mennella I, Fogliano V, Ferracane R et al. (2016) Microencapsulated bitter compounds (from *Gentiana lutea*) reduce daily energy intakes in humans. *Br J Nutr.* PMID: 27829482



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File: ■ Andrographis (*Andrographis paniculata*, Acanthaceae)

■ Blood Glucose

■ Diabetes

HC 032251-686

Date: April 15, 2022

RE: Andrographis Extract Increased GLP-1 Hormone without Inhibiting DPP-4 Enzyme in Prediabetic Participants



Tarigan TJE, Purwaningsih EH, Yusra, et al. Effects of sambiloto (*Andrographis paniculata*) on GLP-1 and DPP-4 concentrations between normal and prediabetic subjects: a crossover study. *Evid Based Complement Alternat Med*. January 15, 2022;2022:1535703. doi:10.1155/2022/1535703.

Type 2 diabetes mellitus (T2DM) currently affects ~415 million people worldwide and is expected to rise to 642 million by 2040. Antidiabetic drugs are available, but many have unfavorable side effects. The hormone incretin is released from the small intestine and into the bloodstream after food intake. This hormone mediates the insulinotropic response; however, this effect decreases in people with T2DM. Phytotherapy has been used for T2DM treatment. *Andrographis* (*Andrographis paniculata*, Acanthaceae) has been traditionally used to treat diabetes, and its andrographolide and flavonoid phytochemicals have been used together for their hypoglycemic effect. Although there have been many studies proving the hypoglycemic effect of andrographolide and flavonoids, there has not been any human study with randomized clinical trial and crossover method for examining andrographis. The authors propose a randomized

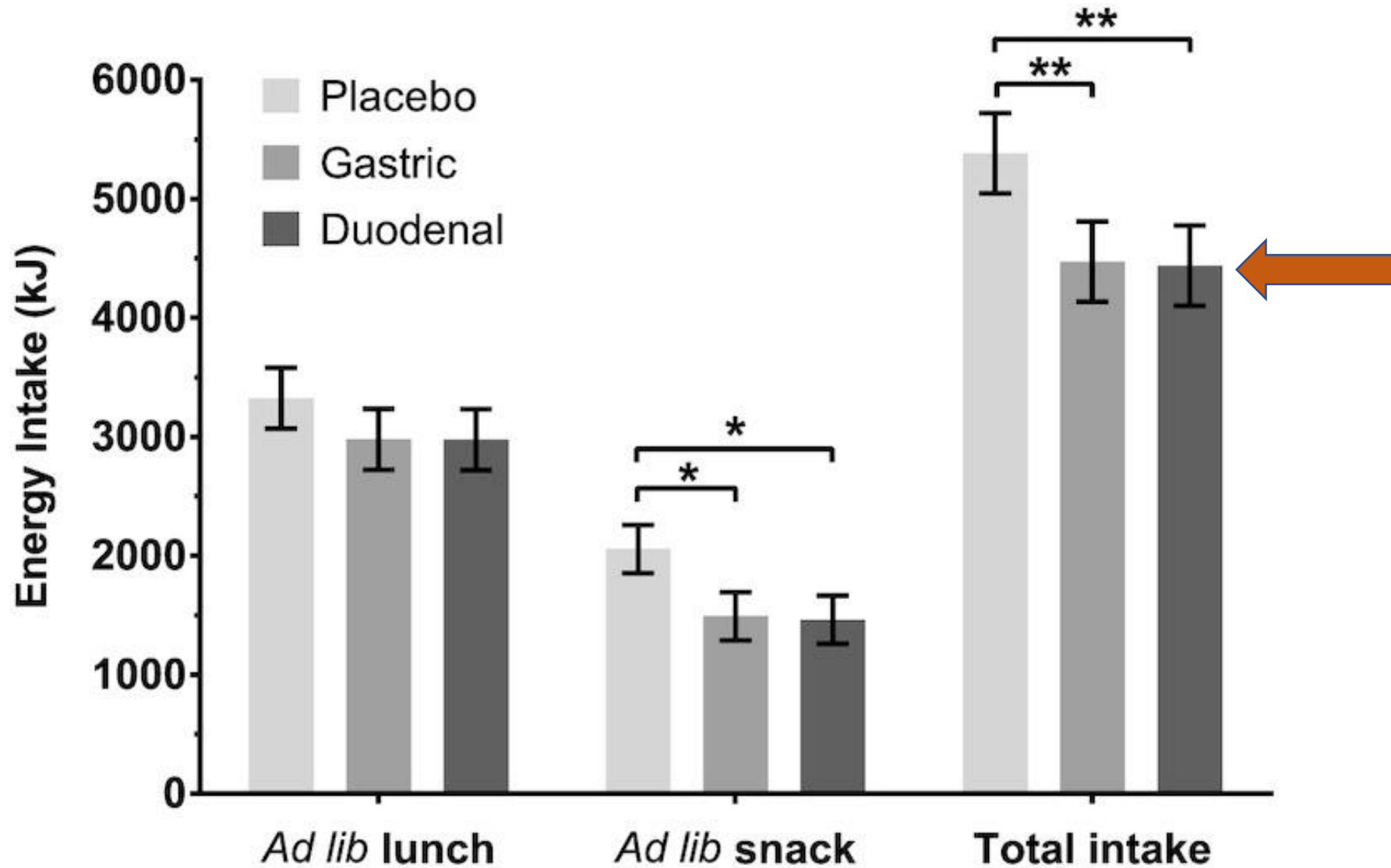
Bitters Regulate Metabolic Function

This all suggests a role for bitter herbs in glucose homeostasis and insulin resistance:

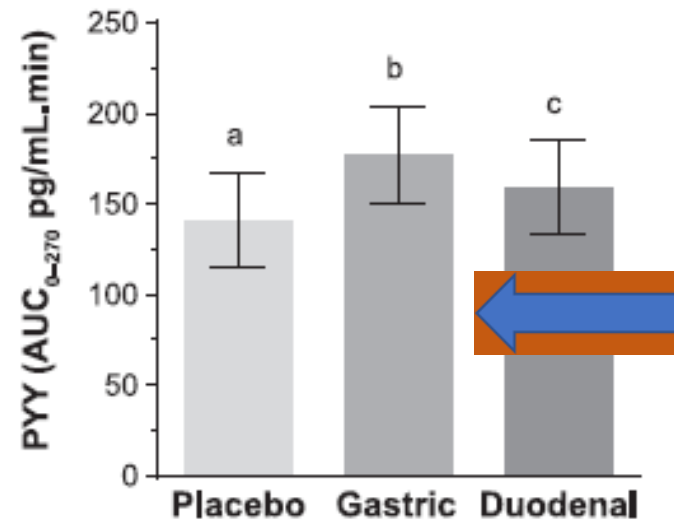
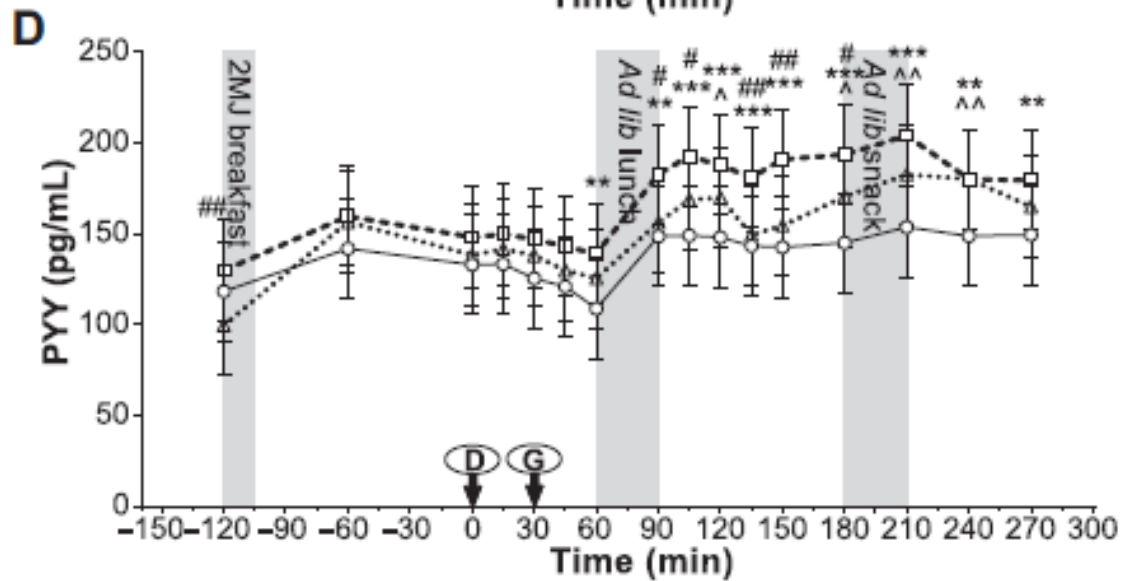
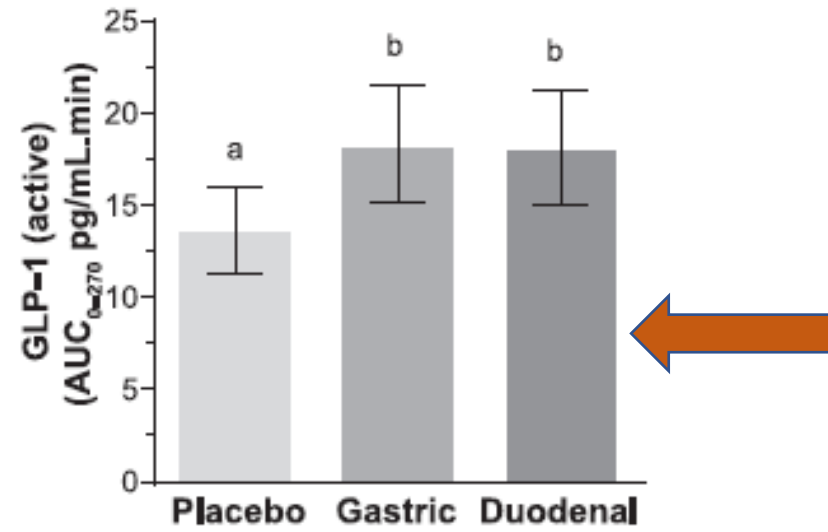
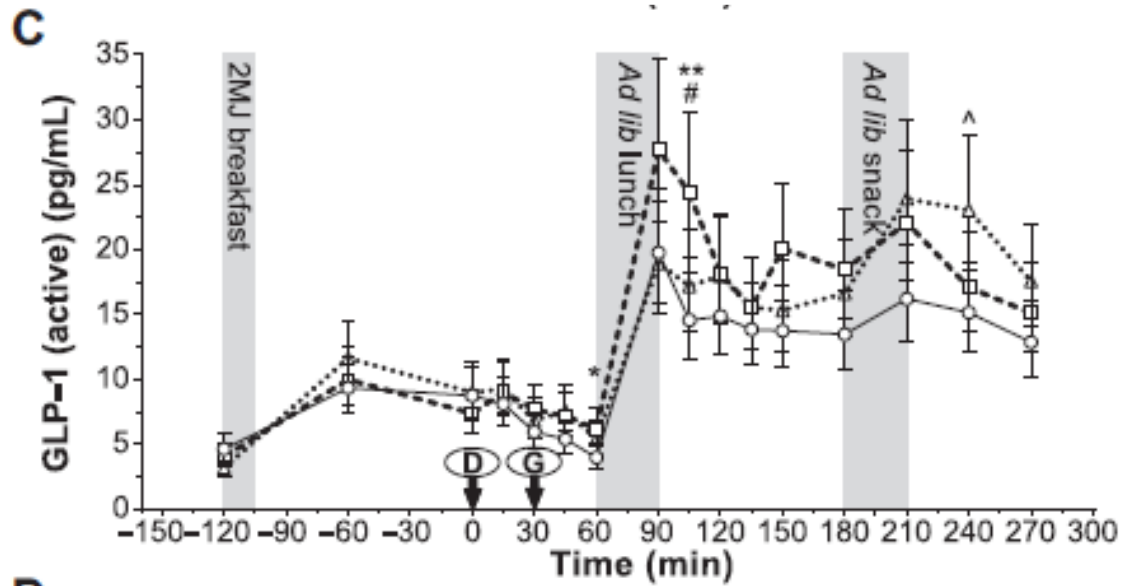
- 94 patients with prediabetes: improvements in BMI, glycaemic control and body fat given just 16 to 48 mg/day of isohumulones (hop bitter acids) as capsules in a double-blind RCT.¹
- Later RCT: liquid hop extract (matured bitter acids 35 mg/d from about 1 g hops) for 12 weeks: significant reduction in visceral fat.²



1. Obara K, Mizutani M, Hitomi Y et al. (2009) Isohumulones, the bitter component of beer, improve hyperglycemia and decrease body fat in Japanese subjects with prediabetes. *Clin Nutr* PMID:19395131
2. Morimoto-Kobayashi Y, Ohara K, Ashigai H et al (2016). Matured hop extract reduces body fat in healthy overweight humans: a randomized, double-blind, placebo-controlled parallel group study. *Nutr J*. PMID: 26960416



Walker EG, Lo KR, Pahl MC 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. *Am J Clin Nutr*. PMID: 35102364



Walker EG, Lo KR, Pahl MC 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. *Am J Clin Nutr*. PMID: 35102364



Effects of gastrointestinal delivery of non-caloric tastants on energy intake: a systematic review and meta-analysis

Tim Klaassen^{1,2} · Daniel Keszthelyi¹ · Freddy J. Troost^{1,2} · Aalt Bast² · Adrian A. M. Masclee¹

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Abstract

Purpose Taste receptors are expressed throughout the gastrointestinal tract. The activation of post-oral taste receptors using tastants could provide a non-invasive treatment option in combating the obesity epidemic. The aim of this review was to examine the effect of post-oral delivery of non-caloric tastants on eating behavior reflected by primary outcome energy intake and secondary outcomes GI symptoms and perceptions and potential underlying mechanisms. This review was conducted according to the PRISMA guidelines for systematic reviews.

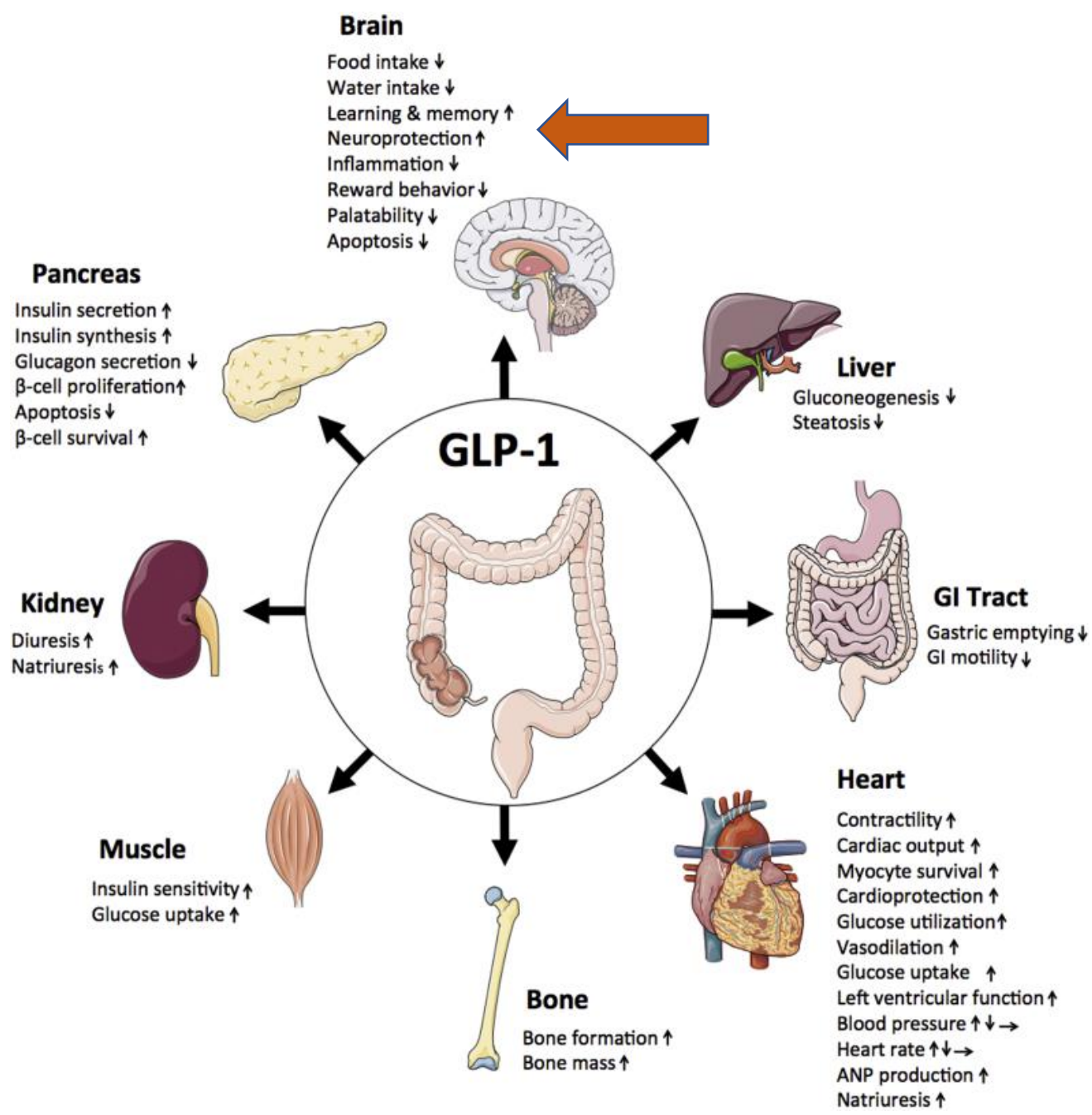
Methods A systematic literature search of the Cochrane, PubMed, Embase, and Medline databases was performed. This systematic review and meta-analysis was registered in the PROSPERO database on 26 February 2020 (ID: CRD42020171182). Two researchers independently screened 11,912 articles and extracted information from 19 articles. If at least two studies investigated the effect of the same taste compound on primary outcome energy intake, a meta-analysis was performed to determine pooled effect sizes.

Results Nineteen papers including healthy volunteers were included. In the 19 papers analyzed, effects of various tastants were investigated in healthy volunteers. Most extensively investigated were bitter tastants. The meta-analysis of effects of bitter tastants showed a significant reduction in energy intake of 54.62 kcal (95% CI – 78.54 to – 30.69, $p=0.0014$).

Conclusions Bitter stimuli are most potent to influence eating behavior. Energy intake decreased after post-oral delivery of bitter tastants. This highlights the potential of a preventive role of bitter tastants in battling the obesity epidemic.



Müller TD, Finan B, Bloom SR et al.(2019)
 Glucagon-like peptide 1 (GLP-1). *Mol Metab.* PMID: 31767182



Bitters Overview

- The multiple benefits of bitters have been rediscovered
- Bitter receptors function not just on the tongue, but also in the rest of the gut and beyond
- Bitter receptors in the gut regulate digestion, blood sugar, metabolism, laxation and satiety



Bitters Overview

- Blending bitters together will have more clinical impact \Rightarrow wider range of bitter receptors impacted: this will help to overcome poor responses due to genotypic and phenotypic variations
- Modern findings support the role of oral bitter herbs in insulin resistance, metabolic syndrome, type 2 diabetes and even weight loss and depression (based on the known activities of CCK, PYY and GLP-1), and perhaps other morbidities

A Final Thought

“Adding bitterness back to your palate could take the bitterness out of your life”

