

The new herbal bitters:

New uses for the most ancient of tastes

TRADITIONAL ROOTS CONFERENCE
MAY 19-21 2017
GLEN NAGEL, ND, RH, (AHG)

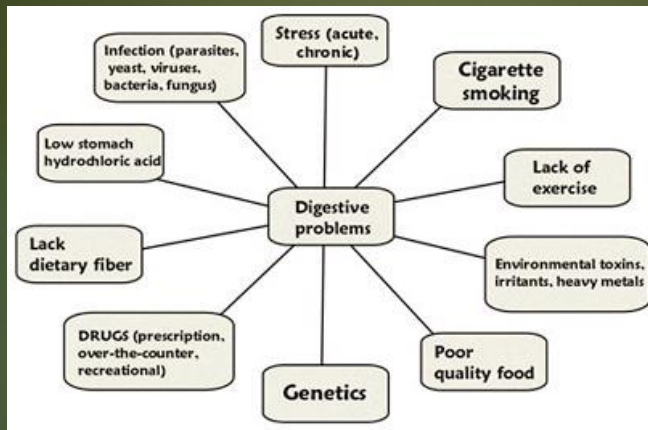


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
























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Digestive Problems are Big Health Concerns



Digestive Concerns: In the News

 <p>Chronic fatigue syndrome: Could altered gut bacteria be a cause?</p> <p>Researchers find that people with chronic fatigue syndrome have an altered gut microbiome, which may shed light on the cause of the elusive condition.</p> <p>28 Jun 2016  251     </p>	 <p>Gut bacteria may have role in bile duct cancer</p> <p>Links between gut bacteria and gastrointestinal cancer are well established. Now, scientists reveal bacteria in the bile duct may also be linked to cancer.</p> <p>27 Jun 2016  147     </p>
 <p>High-fiber diet alters gut bacteria to protect against food allergy</p> <p>A high-fiber diet rich in vitamin A may lower the risk of food allergy, suggest researchers who found that it protected against peanut allergy in mice.</p> <p>26 Jun 2016  524     </p>	 <p>Food pathogen detection via handheld 'nanoflower' biosensor</p> <p>Researchers have created a nanoflower biosensor that recognizes and amplifies signals from E. coli so they can be seen with a simple handheld pH device.</p> <p>19 Jun 2016  141     </p>
 <p>Specific gut bacteria reverse autism-like behavior in mice</p> <p>Could autistic traits be partially controlled by the bacteria in our guts? New research demonstrates that this is a genuine possibility.</p>	 <p>What's the Connection Between Diabetes and Diarrhea?</p> <p>Learn about the connection between diabetes and diarrhea, including the medication and</p>

Top 25 Prescription Drugs Filled 2016

Acid blocker #4

1. Atorvastatin Calcium (generic of Lipitor)
2. Levothyroxine (generic of Synthroid)
3. Lisinopril (generic of Prinivil)
4. **Omeprazole** (generic of Prilosec)
5. Metformin (generic for Glucophage)
6. Amlodipine (generic for Norvasc)
7. Simvastatin (generic for Zocor)
8. Hydrocodone/Acetaminophen (generic for Lortab)
9. Metoprolol ER (generic for Toprol XL)
10. Losartan (generic for Cozaar)
11. Azithromycin (generic for Zithromax)
12. Zolpidem (generic for Ambien)
13. Hydrochlorothiazide (generic for Microzide)
14. Furosemide (generic for Lasix)
15. Metoprolol (generic for Lopressor)
16. **Pantoprazole** (generic for Protonix)
17. Gabapentin (generic for Neurontin)
18. Amoxicillin (generic for Amoxil)
19. Prednisone (generic for Deltasone)
20. Sertraline (generic for Zoloft)
21. Tamsulosin (generic for Flomax)
22. Fluticasone (generic for Flonase)
23. Pravastatin (generic for Pravachol)
24. Tramadol (generic for Ultram)
25. Montelukast (generic for Singulair)

Acid blocker #16

Source: www.lowestmed.com

Special Report: Choosing a PPI

Source: www.consumerreports.org

Consumer Reports

Choosing a PPI To Treat Heartburn, Acid Reflux & GERD

What is GERD?

You may know GERD as heartburn or acid reflux. GERD stands for gastroesophageal reflux disease. It occurs when the ring of muscles between your stomach and your esophagus—the tube that leads from your throat to your stomach—doesn't work right. The muscles either don't close all the way, or they open too often. Then acid from your stomach can back up, or reflux, into your esophagus. This causes that burning feeling that starts in your chest and moves up into your throat.

Treatment

Treatment depends on how often you have heartburn symptoms.

- If you don't get heartburn often, try taking an over-the-counter antacid, like Maalox or Tums. If these do not work, you can try an H2 blocker, like Pepcid or Zantac. They work more slowly than antacids, but they provide relief for a longer time.
- If you have heartburn more than twice a week for more than four weeks and antacids don't help, you need to see a doctor. You probably need a medicine called a proton pump inhibitor (PPI).
- Talk with your doctor about the role that dietary and lifestyle changes can play in alleviating heartburn, too, such as eating smaller meals and not lying down

Taking a PPI for GERD

We compared seven proton pump inhibitors (PPIs). This is what we found:

All PPIs work well. All the PPIs completely relieved symptoms for about seven out of 10 people within four weeks. And they all healed damage to the esophagus in about eight out of 10 people within eight weeks.

All PPIs are generally safe for short-term use. PPIs can cause some minor side effects, such as headache and diarrhea. But most people can use PPIs without problems. And most need a PPI for only a few months. If PPIs are used for more than a few months, there is a higher risk of pneumonia, infection, and fractures.

PPIs differ a lot in price.

Over-the-counter PPIs cost about \$17–\$24 per month. Prescription generic PPIs cost \$58–\$163 per month. Prescription brand-name PPIs cost \$183–\$374 per month.

Our advice:

We chose the following as *Consumer Reports Best Buy Drugs*. You can get them without a prescription:

- Generic omeprazole OTC

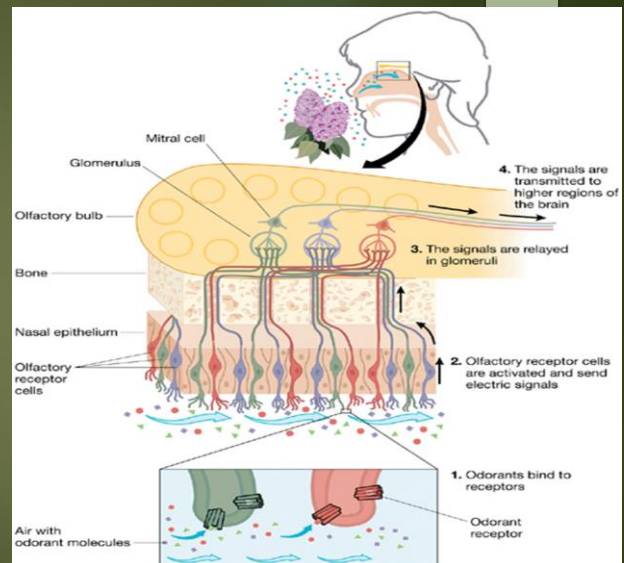
Herbal Organoleptics: The Sensory Experience

- ▶ **Organoleptic Defined:**
- ▶ Making an impression upon an organ. Said of the effect or impression produced by any substance on the organs of touch, taste or smell, and also on the organism as a whole.
- ▶ Herbs work well to stimulate the senses and may derive much of their therapeutic action to taste and smell.
- ▶ Bitter tastes are common in herbs

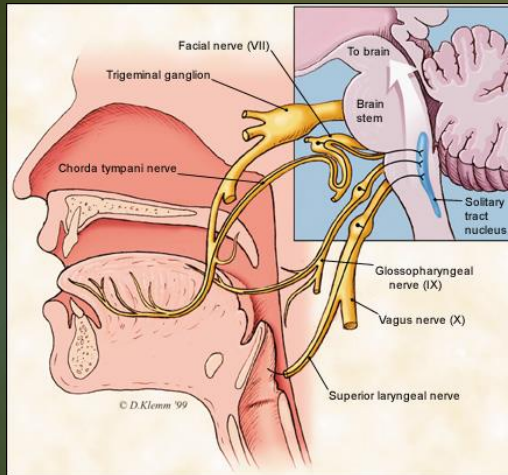


The Sense of Smell and Taste

- ▶ Each odor molecule fits like a lock and key onto a specific receptor site on the olfactory epithelium. When stimulated the epithelium triggers nerve cells electrical impulses to stimulate the olfactory bulb in the brain.
- ▶ The olfactory bulb stimulates impulses to the gustatory center for taste and the amygdala where emotions and memory are stored.

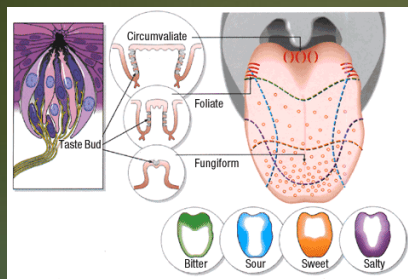


The Senses of Taste and Smell



This is why that a simple smell can effect mood, blood pressure, heart rate, breathing, memory, hormone levels and stress levels.

The Five Basic Tastes



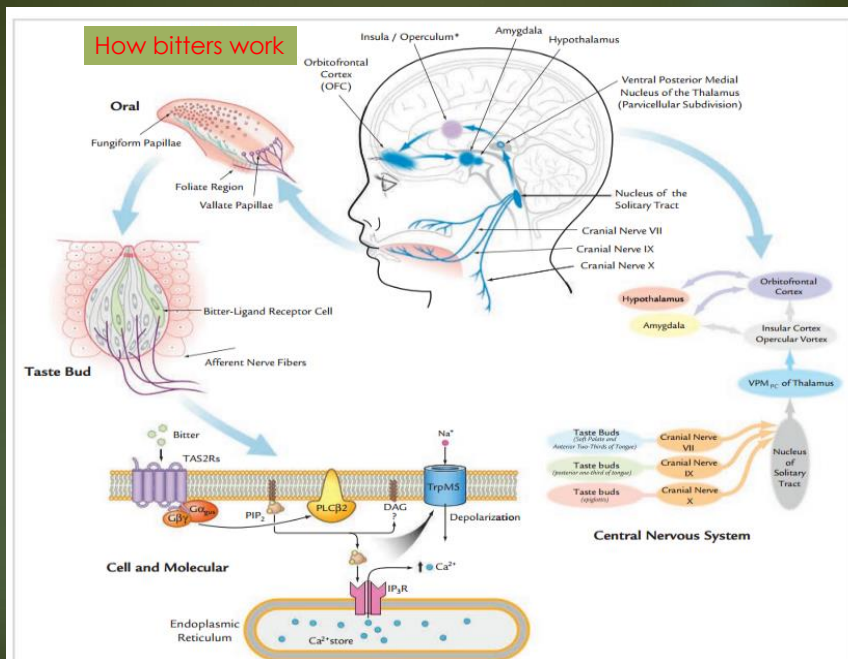
5 Basic Tastes



How do bitters work?

- Taste buds are distributed in distinct fields in the oral, pharyngeal, and laryngeal epithelia, with each field innervated by a different cranial nerve branch.
- The taste buds of the laryngeal epithelium are thought to be involved more with protection of the airways.
- Taste receptors have also been identified in a variety of non gustatory tissues, such as the gut, where they have been proposed to play a role in nutrient and toxin sensing.
- The taste signals course through the brain and provide input to circuits that sub serve various functions, such as motor and physiological reflexes, discriminative perception, and affective processing.

Clinical Therapeutics/Volume 35, Number 8, 2013

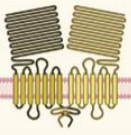
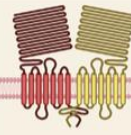
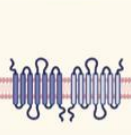
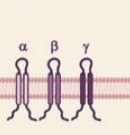
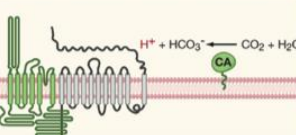


Clinical Therapeutics/Volume 35, Number 8, 2013

The bitter reflex and its Gastrointestinal implications

- ▶ When a bitter substance is recognized by bitter receptors on the tongue, a chain of neural and endocrine events begins, labeled as the "bitter reflex." Mediated by the release of the gastric hormone gastrin, this reflex results in an overall stimulation of digestive function, which over time strengthens the structure and function of all digestive organs (liver, stomach, gallbladder, pancreas, etc.)
- ▶ Starting in your mouth, you'll notice that your salivary glands have increased their output of enzyme-rich saliva, helping to break down complex starches into smaller and more easily digested oligosaccharides.
- ▶ In the stomach, the hormone gastrin has stimulated the secretion of hydrochloric acid.
- ▶ The acidity helps break down protein, enhances the bioavailability of many minerals (especially calcium) and destroys any harmful microbes present in your food.

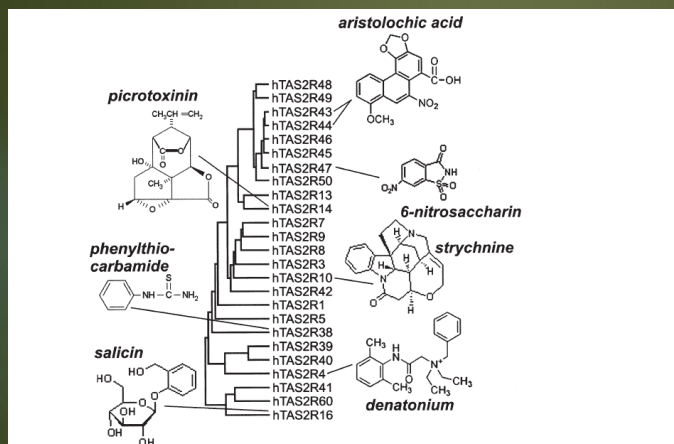
Many types of Mammalian Taste Receptors

Mammalian taste receptors and cells				
Umami	Sweet	Bitter	Sodium	Sour and carbonation cells
				
T1R1+T1R3 L-glutamate L-amino acids glycine L-AP4 Nucleotide enhancers IMP, GMP, AMP	T1R2+T1R3 Sugars Sucrose, fructose, glucose Artificial sweeteners saccharin, acesulfame K, aspartame, cyclamate D-amino acids D-alanine, D-serine, D-phenylalanine Glycine Sweet proteins Monellin, thaumatococin	~30 T2Rs Cycloheximide (mT2R5) Denatonium (mT2R6, hT2R4) Salicin (hT2R16) ← From Willow PTC (hT2R38) Saccharin (hT2R43, hT2R44) Quinine strychnine atropine ← Botanical Toxins	ENaC Low NaCl Sodium salts	PKD2L1 Acids Citric acid Tartaric acid HCl CA IV Carbonated drinks $H^+ + HCO_3^- \rightarrow CO_2 + H_2O$

Many type of bitter receptors

- ▶ Type 2, bitter receptors were first characterized in 2000: *TAS2R1* – *TAS2R50*, and *TAS2R60*. There are 50 + type of bitter receptors as opposed to 2-3 types of sweet receptors
- ▶ The TAS2R proteins function as bitter taste receptors. There are 43 human *TAS2R* genes
- ▶ Gustducin is the most common taste G protein subunit, having a major role in TAS2R bitter taste reception.
- ▶ Gustducin and Transducin are G proteins and have been shown to be structurally and functionally similar, leading researchers to believe that the sense of taste evolved in a similar fashion to the sense of sight

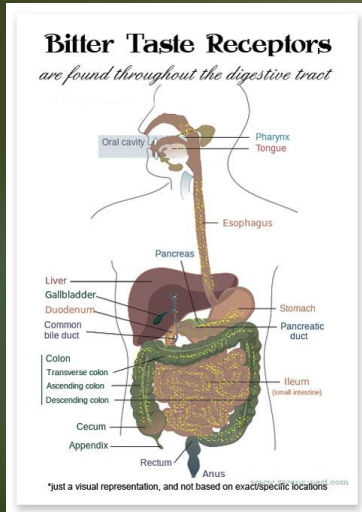
Bitter receptors



- ▶ Agonist for human bitter taste receptors are structurally diverse
- ▶ Individual bitter agents stimulate specific bitter receptors.

Cellular and Molecular Life Sciences 63: 1501-1509, 2006

Bitter receptors are found all over the body



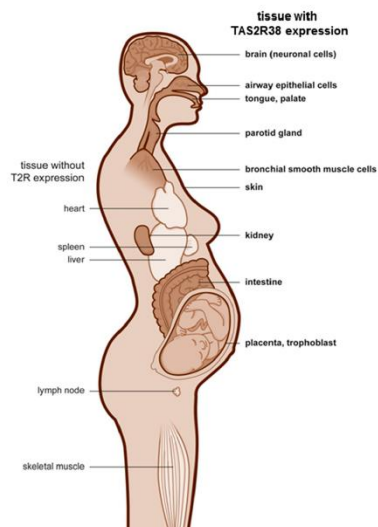
- ▶ Old thought was that bitter receptors were on the back of the tongue only
- ▶ Now we know bitter receptors are found all over the digestive tract and beyond
- ▶ Recent research has found them in the lungs, bronchi and in the placenta and thyroid gland
- ▶ Bitters receptors seem to be important to humans!

Polymorphisms in bitter taste receptor genes

- ▶ An important question for human bitter taste research is how individualized the perception of different bitter compounds is. It appears that humans vary greatly with regard to bitterness perception of some bitter compounds
- ▶ As more and more TAS2Rs are being deorphanized and therefore become accessible for functional analyses of receptor variants, the number of known functional polymorphisms will increase considerably in the future.
- ▶ It will then be very interesting to see how personal bitter taste perception might influence dietary habits and, ultimately, health.

Cellular and Molecular Life Sciences 63: 1501-1509, 2006

HUMAN TISSUE EXPRESSING TAS2R38 RECEPTORS



Molecules 2016, 21, 306

F1000Reports
BIOLOGY

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Taste isn't just for taste buds anymore

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Taken together, the findings suggest that the taste transduction cascade is not restricted to taste per se or even to systems regulating food intake. The receptors mediating taste transduction evolved early in the vertebrate lineage, and were adopted widely as a **chemodetection system** in a variety of organ systems. Questions still remain as to what the natural ligands are for many of the nongustatory functions of the "taste" transduction system

F1000 Biology Reports 2011, 3:20

Bitter taste perception Pre Neanderthal

biology
letters
Evolutionary biology

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doi:10.1098/rbl.2009.0532
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Bitter taste perception in Neanderthals through the analysis of the *TAS2R38* gene

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The bitter taste perception (associated with the ability or inability to taste phenylthiocarbamide) is mediated by the *TAS2R38* gene. Most of the variation in this gene is explained by three common amino-acid polymorphisms at positions 49 (encoding proline or alanine), 262 (alanine or valine) and 296 (valine or isoleucine) that determine two common isoforms: proline–alanine–valine (PAV) and alanine–valine–isoleucine (AVI). PAV is the major taster haplotype (heterozygote and homozygote) and AVI is the major non-taster

The most extensively studied taste variation in humans is sensitivity to a bitter substance called phenylthiocarbamide (PTC). Although approximately 75 per cent of the world population perceives this substance as intensely bitter, it is virtually tasteless for the remaining 25 per cent of the population (Kim & Drayna 2004). This is owing to a dominant ‘taster’ allele that shows a similar frequency to the recessive ‘non-taster’ allele. PTC itself is not found in any vegetable, but chemically similar substances that produce an identical response to PTC are present in many plant foods (including Brussels sprouts, cabbage, broccoli and others). It was discovered (Kim *et al.* 2003) that most of the variation in PTC sensitivity is related to polymorphisms at the *TAS2R38* gene, a single 1002 bp coding exon that encodes a 333-amino-acid, G-protein-coupled receptor. The *TAS2R38* gene has three amino-acid changes in high frequencies that determine only five main haplotypes. These polymorphisms are found at position 49 (encoding proline or alanine), 262 (alanine or valine) and 296 (valine or isoleucine) of the gene. The two most common haplotypes are proline–alanine–valine (PAV) and alanine–valine–isoleucine (AVI). PAV is the major taster haplotype (carrying one or two copies), and AVI is the major non-taster haplotype (carrying two copies). AVI/PAV heterozygotes have slightly less sensitivity to PTC (Drayna 2005). Of the three common variants, the nucleotide substitution at the amino-acid residue 49 (A49P) shows the strongest association with taster status; a proline at that position always implies PTC taste perception (Drayna 2005). Other additional haplotypes, AAV, PVI and AAI,



Biol. Lett. (2009) 5, 809–811

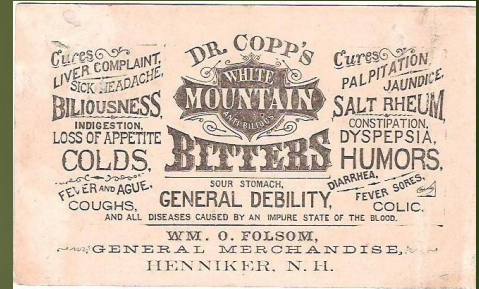
Bitter taste perception pre Neanderthal Study Summary:

- The most extensively studied taste variation in humans is sensitivity to a bitter substance called phenylthiocarbamide (PTC)
- Neanderthals were a hominid species living in Europe and Western Asia from approximately half a million years ago to approximately 28,000 years ago
- The amplified and sequenced the *TAS2R38* amino acid 49 in the virtually uncontaminated Neanderthal sample of El Sidron 1253 and have determined that it was heterozygous
- Thus, this Neanderthal was a taster individual, although probably slightly less than a PAV homozygote. This indicates that variation in bitter taste perception pre-dates the divergence of the lineages leading to Neanderthals and modern humans
- ▶ Neanderthal A49P heterozygote is that this polymorphism pre-dates the split of Neanderthal and modern human lineages, known to have been at least half a million years ago

Biol. Lett. (2009) 5, 809–811

Herbal bitters: Historical

- ▶ The earliest origins of bitters can be traced back as far as the ancient Egyptians, who may have infused medicinal herbs in jars of wine.
- ▶ This practice was further developed during the Middle Ages, where the availability of distilled alcohol coincided with a renaissance in pharmacognosy.
- ▶ Many of the various brands and styles of digestive bitters made today reflect herbal stomachic and tonic preparations whose roots are claimed to be traceable back to Renaissance era pharmacopeia and traditions.
- ▶ By the 19th century, the British practice of adding herbal bitters (used as preventive medicines) to Canary wine had become immensely popular in the former American colonies.
- ▶ By 1806, American publications referenced the popularity of a new preparation termed *cocktail*, which was described as a combination of "a stimulating liquor, composed of spirits of any kind, sugar, water, and bitters."

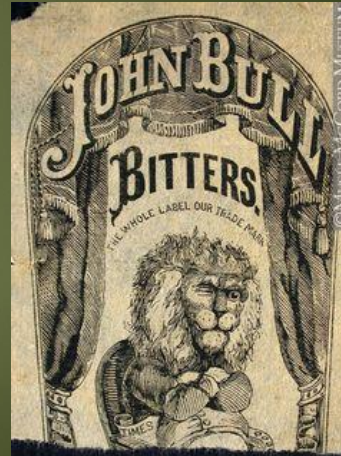


Herbal bitters: A long history of Use

- ▶ Has a long historical use as medicine and drinks
- ▶ Any plant that tastes bitter is bitter
- ▶ Many herbal drinks are bitter
- ▶ Many bitters are also classified as a tonic.
- ▶ You know when it is bitter !
- ▶ Rediscovered recently in food and medicine.
- ▶ Many new studies on the action of bitters and effects on physiology.

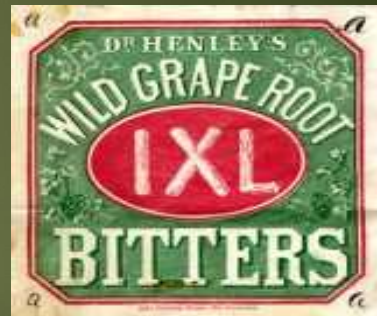
Historical Ideas about bitters

- ▶ The bitters are considered as tonic and stomach. To improve the appetite when taken in moderation. The best time is early in the morning or an hour before meals.
- ▶ From Dick's Encyclopedia of Practical Receipts and Processes (1872)
- ▶ The bitters only work if you taste them.



Historical Sayings about bitters

- ▶ Sweet to the taste buds, bitter to the stomach
- ▶ Bitter to the tongue, then sweet to the stomach
- ▶ The bitters are a tonic for all digestion and especially promote acid secretion



Traditional indications for bitters

- ▶ Loss of appetite, low HCL
- ▶ Indigestion, bloating, gas
- ▶ Nausea, diarrhea, constipation
- ▶ Abdominal distention
- ▶ Malnutrition, malabsorption
- ▶ Weakness, pale skin with edema
- ▶ Yellow or white tongue coating
- ▶ Atonic digestion and elimination
- ▶ Depression and or mood disorders
- ▶ Digestive issues that come with aging.

Traditional contra-indications of bitters

CONTRA-INDICATIONS

- ▶ Avoid in cases of acute GI inflammation, irritation
- ▶ Avoid in pregnancy
- ▶ Avoid in children under 5

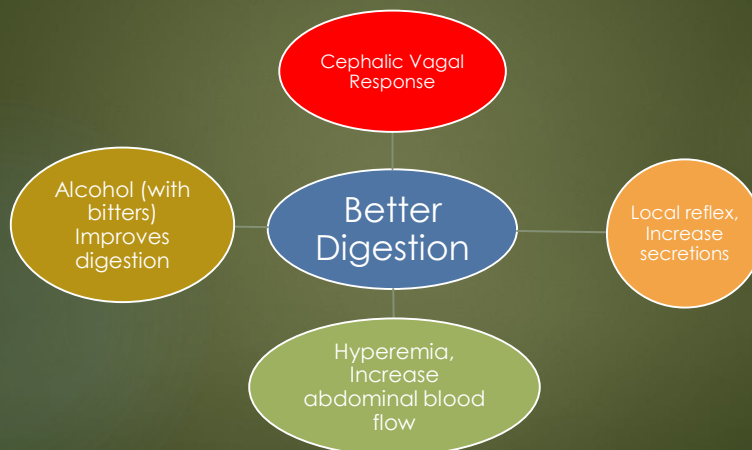


Types of Herbal bitters

- ▶ True bitters: Only bitter
 - ▶ *Centaurium umbellatum*
 - ▶ *Gentiana lutea*
 - ▶ *Hydrastis canadensis*
 - ▶ *Mahonia aquifolium*
 - ▶ *Aloe spp.* Bitter Aloe
 - ▶ *Eupatorium perfoliatum*
 - ▶ *Menyanthes trifoliata*
 - ▶ Cinchona bark
 - ▶ Quassia bark
- ▶ Aromatic bitters: bitter with flavor
 - ▶ *Artemisia absinthium*
 - ▶ *Achillea millefolium*
 - ▶ *Humulus lupulus*
- ▶ Nutritional bitters with Prebiotics
 - ▶ *Taraxacum*
 - ▶ *Articum*
 - ▶ *Inula*
 - ▶ *Angelica*
 - ▶ *Cynara*



Current summary of how bitters Improve digestion



New bitter concepts

- ▶ The bitter receptors TR2 a family of G protein coupled receptors
- ▶ Can sense over 100 types of bitters based on testing
- ▶ Can have effects without tasting the bitterness
- ▶ Chronic inflammation can over express TR2 receptors leading to adverse response to bitters
- ▶ The bitters stimulate natural incretins and hence stimulate insulin and lower glucose
- ▶ The bitters may act directly as endocrine triggers, by passing the CNS
- ▶ Stimulate Hyperemia increasing GI blood flow
- ▶ The bitter may lead to less obesity and improve metabolic syndrome via increase fullness, and hormone stimulation
- ▶ Lack of bitter sensitivity may contribute to alcoholism *



The bitter truth: It is good for us!

- ▶ The effect of bitters also extends to the pancreas. With bitters, digestive enzyme secretions are increased, helping to promote the complete breakdown of nutrients into their absorbable units, preventing gas formation when large molecules are acted upon by bacteria further down the small intestine.
- ▶ The complete breakdown of proteins is particularly important, as the cross reactivity of immune cells between undigested protein molecules and intestinal cells plays an important role in the etiology of conditions such as celiac disease and allergies
- ▶ Insulin and glucagon secretions are stimulated, helping to normalize blood sugar levels.
- ▶ Our cravings for sweetness may mask cravings for bitterness.
- ▶ Thus, the taste of bitter can be used to strengthen the most fundamental aspect of our health—the ability to extract the nutrients from our foods and nourish our bodies. Over time, they will lessen symptoms of poor digestive function such as gas and bloating, constipation, loose stools and food allergies; enhance vitamin and mineral absorption; promote balanced blood sugar levels; protect the liver and strengthen eliminatory function; moderate inflammatory damage to the gut wall; and reduce the incidence of allergic.

New actions for bitters

- ▶ Blood Sugar Support
 - ▶ Incretin effect
 - ▶ Probiotics from bitter herbs
- ▶ Cardiovascular effects
 - ▶ Lipid Moderating
 - ▶ Metabolic syndrome
- ▶ Supports decrease craving for alcohol
- ▶ Thyroid Balance
 - ▶ The bitter receptors found in thyrocytes
 - ▶ Can block or enhance TSH production
- ▶ Vascular effect Increase gut circulation, increase BP
- ▶ Neuronal effects
 - ▶ Stimulate endocrine hormones via gut
 - ▶ Improved digestion , absorption
 - ▶ Appetite stimulant , but increase satiety and weight loss
- ▶ Chronic Inflammation
 - ▶ Pro inflammatory compounds serve to over express T2Rs. Leading to adverse bitter response
 - ▶ The bitters can down regulate Tumor Necrosis factor receptors

Review Article

Bitters: Time for a New Paradigm

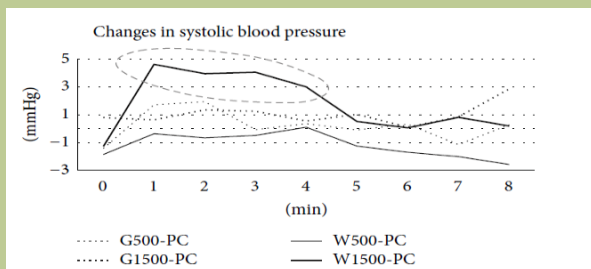
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gastric phase. These findings provide the platform for a new evidence-based paradigm.

ns Attribution
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Bitters can influence all phases of digestion

- Cephalic, Taste
- Gastric
- Intestinal

Evidence-Based Complementary and Alternative Medicine

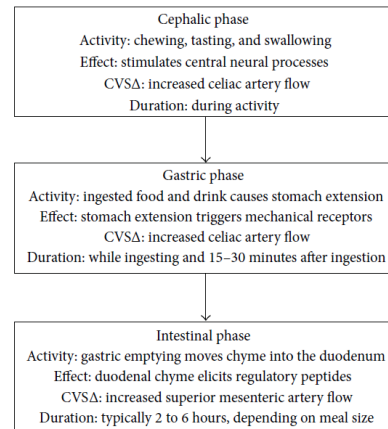


FIGURE 1: The three phases of digestion. CVSA: cardiovascular system change.

Source: Bitters time for a new paradigm://dx.doi.org/10.1155/2015/670504

Facial reactions to bitter foods

Appetite. 2013 Dec;71:178-86. doi: 10.1016/j.appet.2013.08.013. Epub 2013 Aug 30.

Facial affective reactions to bitter-tasting foods and body mass index in adults.

Garcia-Burgos D¹, Zamora MC.

Author information

Abstract

Differences in food consumption among body-weight statuses (e.g., higher fruit intake linked with lower body mass index (BMI) and energy-dense products with higher BMI) has raised the question of why people who are overweight or are at risk of becoming overweight eat differently from thinner people. One explanation, in terms of sensitivity to affective properties of food, suggests that palatability-driven consumption is likely to be an important contributor to food intake, and therefore body weight. Extending this approach to unpalatable tastes, we examined the relationship between

aversive react
stimuli, even a
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reports. Forty
participants w
high BMI parti
and incentive
reacted to bitt
differences be
facial reactions

The results indicated that high BMI (Body mass index) participants reacted to bitter stimuli showing more profound changes from baseline in neutral and disgust facial expressions compared with low BMI. No differences between groups were detected from the subjective pleasantness and familiarity.

to bitter food, apart from taste responsiveness, can predict differences in BMI.

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D=5.8). On the basis of BMI,
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red with low BMI. No
to examine how affective

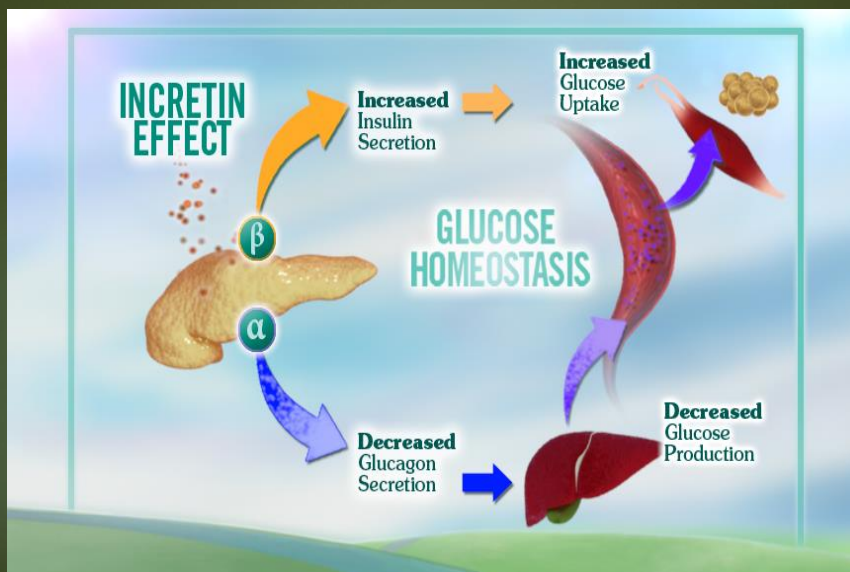
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KEYWORDS: Affective facial reaction; Bitter food; Body mass index; Overweight; Taste responsiveness

THE INCRETIN EFFECT

- ▶ This phenomenon has been dubbed the 'incretin effect' and is estimated to account for approximately 50-70% of the total insulin secreted following oral glucose administration.
- ▶ Thus, incretins are hormones that are secreted from the gastrointestinal tract into the circulation in response to nutrient ingestion that enhance glucose-stimulated insulin secretion.
- ▶ The term 'incretin' was subsequently used to denote these glucose-lowering, intestinal-derived factors
- ▶ The bitters stimulate natural incretins and hence stimulate insulin and lower glucose

The bitters stimulate natural incretins



Research on bitters

OPEN ACCESS Freely available online PLOS one

Bitter Taste Receptors Influence Glucose Homeostasis

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Abstract: TAS1R- and TAS2R-type taste receptors are expressed in the gustatory system, where they detect sweet- and bitter-tasting stimuli, respectively. These receptors are also expressed in subsets of cells within the mammalian gastrointestinal tract, where they mediate nutrient assimilation and endocrine responses. These findings suggest that a functionally compromised TAS2R receptor negatively impacts glucose homeostasis, providing an important link between alimentary chemosensation and metabolic imbalance.

Background: TAS1R- and TAS2R-type taste receptors are expressed in the gustatory system, where they detect sweet- and bitter-tasting stimuli, respectively. These receptors are also expressed in subsets of cells within the mammalian gastrointestinal tract, where they mediate nutrient assimilation and endocrine responses. These findings suggest that a functionally compromised TAS2R receptor negatively impacts glucose homeostasis, providing an important link between alimentary chemosensation and metabolic imbalance.

Gut microbiota fermentation of prebiotics increases satiety and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal¹⁻³

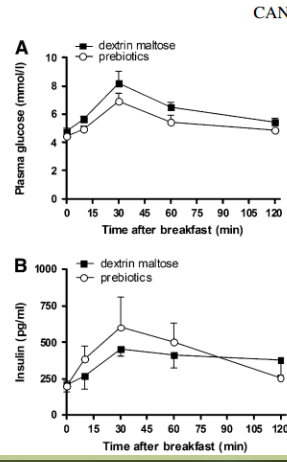
Patrice D Cani, Elodie Lecourt, Evelyne M Dewulf, Florence M Sohet, Barbara D Pachikian, Damien Naslain, Fabienne De Backer, Audrey M Neyrinck, and Nathalie M Delzenne

ABSTRACT

Background: We have previously shown that gut microbial fermentation of prebiotics promotes satiety and lowers hunger and energy intake in humans. Together with recent findings by others provide evidence that prebiotics could be a useful tool for controlling food intake and glucose homeostasis and promising agents for maintaining or restoring both glucose and energy homeostasis.

Results: We show that the prebiotic treatment increased breath-hydrogen excretion (a marker of gut microbiota fermentation) by ~3-fold and lowered hunger rates. Prebiotics increased plasma glucagon-like peptide 1 and peptide YY concentrations, whereas postprandial plasma glucose responses decreased after the standardized meal. The areas under the curve for plasma glucagon-like

associated risk factors. Recent studies provide evidence for a link between dietary composition of the gut microbiota and metabolic syndrome. Prebiotics in the present study significantly increased satiety index and energy intake. In addition to these findings, these human studies suggest that gut microbiota and body weight regulation mechanisms in humans have previously been shown to be modulated by GLP-1, glucagon-like peptide YY (PYY), and other gut peptides.



Am J Clin Nutr 2009;90:1236-43

Bitters and Thyroid Function

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Published online 2014 Oct 23. doi: [10.1096/fj.14-262246](https://doi.org/10.1096/fj.14-262246)

PMCID: PMC4285546

TAS2R bitter taste receptors regulate thyroid function

Adam A. Clark,^{†,1} Cedrick D. Dotson,^{*,2} Amanda E. T. Elson,^{†,3} Anja Voigt,[§] Ulrich Boehm,[¶] Wolfgang Meyerhof,[§] Nanette J. Steinle,[‡] and Steven D. Munger^{†‡,1,4}

Abstract

Dysregulation of thyroid hormones triiodothyronine and thyroxine (T3/T4) can impact metabolism, body composition, and development. Thus, it is critical to identify novel mechanisms that impact T3/T4 production. We found that type 2 taste receptors (TAS2Rs), which are activated by bitter-tasting compounds such as those found in many foods and pharmaceuticals, negatively regulate thyroid-stimulating hormone (TSH)-dependent Ca^{2+} increases and TSH-dependent iodide efflux in thyrocytes. Immunohistochemical *Tas2r*-dependent reporter expression and real-time PCR analyses reveal that human and mouse thyrocytes and the Nthy Ori 3-1 human thyrocyte line express several TAS2Rs. Five different agonists for thyrocyte-expressed TAS2Rs reduced TSH-dependent Ca^{2+} release in Nthy Ori 3-1 cells, but not basal Ca^{2+}

Our findings indicate that TAS2Rs couple the detection of bitter-tasting compounds to changes in thyrocyte function and T3/T4 production. Thus, TAS2Rs may mediate a protective response to over ingestion of toxic materials and could serve as new targets for therapeutic treatment of hypo- or hyperthyroidism.

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associated
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Bitters and Alcohol Consumption

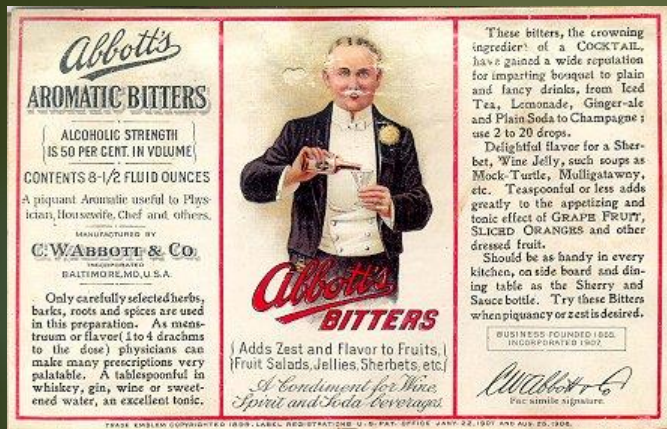
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 31, No. 2
February 2007

Functional Variants in *TAS2R38* and *TAS2R16* Influence Alcohol Consumption in High-Risk Families of African-American Origin

In summary, taste perception is a complex trait influenced by numerous genes. Further, there are European American and African-American population differences in the frequency of these variants. We have observed modest findings with 2 genes, which contribute to bitter-taste sensitivity and influence alcohol consumption. As alcohol consumption is a necessary precursor leading to alcohol dependence, taste perception may represent one of the many pathways that contribute to the development of or protection against alcohol dependence.

Bitters in Formulation



Abbott's
AROMATIC BITTERS

ALCOHOLIC STRENGTH
IS 50 PER CENT. IN VOLUME

CONTENTS 8-1/2 FLUID OUNCES

A piquant Aromatic useful to Physician, Housewife, Chef and, others.

MANUFACTURED BY
C. W. ABBOTT & CO.
BALTIMORE, MD., U.S.A.

Only carefully selected herbs, barks, roots and spices are used in this preparation. As menstruum or flavor (1 to 4 drachms to the dose) physicians can make many prescriptions very palatable. A tablespoonful in whiskey, gin, wine or sweetened water, an excellent tonic.

These bitters, the crowning ingredient of a COCKTAIL, have gained a wide reputation for imparting bouquet to plain and fancy drinks, from Iced Tea, Lemonade, Ginger-ale and Plain Soda to Champagne; use 2 to 20 drops.

Delightful flavor for a Sherbet, Wine Jelly, such soups as Mock-Turtle, Mulligatawny, etc. Teaspoonful or less adds greatly to the appetizing and tonic effect of GRAPE FRUIT, SLICED ORANGES and other dressed fruit.

Should be as handy in every kitchen, on side board and dining table as the Sherry and Sauce bottle. Try these Bitters when piquancy or zest is desired.

BUSINESS FOUNDED 1822.
INCORPORATED 1897.

W. Abbott & Co.
Fac simile signature.

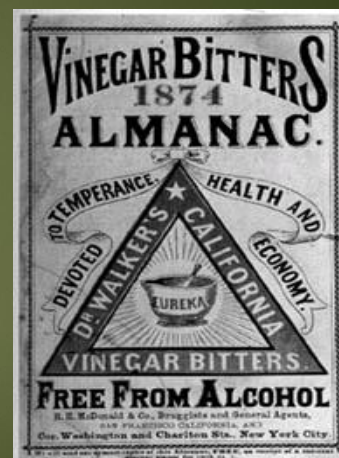
TRADE MARK. COPYRIGHT © 1899. LABEL REGISTRATION U. S. PAT. OFFICE. JAN. 22, 1907 AND AUG. 25, 1908.

Abbott's BITTERS
(Adds Zest and Flavor to Fruits.)
(Fruit Salads, Jellies, Sherbets, etc.)
A Condiment for Wine, Spirit and Soda Beverages.

- ▶ True bitters are commonly and historically mixed in combination with aromatic and carminative herbs
- ▶ Lessens the ability of bitters to cause bowel cramping
- ▶ Warms the formula
- ▶ Commonly use mints, fennel, anise, calamus, Ginger or aromatic bitter herbs in combinations

Dosing bitters

- ▶ Generally small doses , repeated frequently
- ▶ 15-30 drops of extract, or 0.5-1.0 ml
- ▶ Larger doses may improve action , but increase slowly
- ▶ Before meals or after
- ▶ Present to the taste buds as tea or extract
- ▶ Capsule and tablet of bitters have been found to be useful for GI tract bitter receptors and general systemic effects



VINEGAR BITTERS
1874
ALMANAC.

TO TEMPERANCE. HEALTH AND ECONOMY.

DEVOTED TO WALKER'S CALIFORNIA

EUREKA

VINEGAR BITTERS

FREE FROM ALCOHOL

J. B. WALKER & CO., PROPRIETORS AND SOLE AGENTS,
SAN FRANCISCO, CALIFORNIA, U.S.A.

Cor. Washington and Chariton Sts., New York City.

Our famous bitters (Eupeptic)



Wormwood



Gentian

Gentiana lutea (Gentian)

- ▶ **Common names:** Bitter Root, Bitterwort, Gall Weed, Gentiana, Gentianae radix, Pale Gentian, Stemless Gentian, Yellow Gentian, Wild Gentian, Qin Jiao .
- ▶ **Family:** Gentianaceae
- ▶ Listed in the USP 1820-1955, and the NF 1955-1965
- ▶ **Medicinal parts:** root and rhizome
- ▶ **Preparations:** dried root may be decocted or powdered and encapsulated. Dried or fresh root may be tinctured



Gentiana lutea

CHEMICAL CONSTITUENTS

- ▶ *Gentiopicroside*-a bitter principle. One of the most bitter substances known.. Comprises 1-2% of the fresh root.
- ▶ *Genistic Acid* (Genistin) - an organic acid
- ▶ *Tannic acid* - tiny amounts
- ▶ *Quinnic acid* - minute amounts
- ▶ Isovitexin
- ▶ Vanilic acid
- ▶ Gentian contains very little tannin and is considered a pure peptic bitter.

Chromatographic Evaluation and Characterization of Components of Gentian Root Extract Used as Food Additives

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^aCollege of Pharmaceutical Sciences, Matsuyama University; 4-2 Bunkyo-cho, Matsuyama, Ehime 790-8578, Japan:

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Received October 9, 2015; accepted November 9, 2015

Gentian root extract is used as a bitter food additive in Japan. We investigated the constituents of this extract to acquire the chemical data needed for standardized specifications. Fourteen known compounds were isolated in addition to a mixture of gentisin and isogentisin: anofinic acid, 2-methoxyanofinic acid, furan-2-carboxylic acid, 5-hydroxymethyl-2-furfural, 2,3-dihydroxybenzoic acid, isovitexin, gentiopicroside, loganic acid, sweroside, vanillic acid, gentisin 7-*O*-primeveroside, isogentisin 3-*O*-primeveroside, 6'-*O*-glucosylgentiopicroside, and swertiajaposide D. Moreover, a new compound, loganic acid 7-(2'-hydroxy-3'-*O*- β -*D*-glucopyranosyl)benzoate (1), was also isolated. HPLC was used to analyze gentiopicroside and amarogentin, defined as the main constituents of gentian root extract in the List of Existing Food Additives in Japan.

Key words gentian root extract; *Gentiana lutea*; food additive; bittering agent; iridoid

Gentian Root

ACTIONS

- ▶ Cholagogue
- ▶ Bitter tonic
- ▶ Gentian is stimulating to digestive organs, mucosal tissues, and portal circulation.

INDICATIONS

- ▶ GI atony, poor digestion, low stomach acidity.*
- ▶ Portal Congestion
- ▶ General GI debility, atony, flatulence, anorexia *

CONTRAINDICATIONS

- ▶ Avoid in cases of acute GI inflammation
- ▶ Avoid in pregnancy



Gentian Root: *Specific Indications* (Felter Materia Medica 1922)

- ▶ **Action and Therapy.**—One of the best of the simple bitter tonics. However, large doses can produce nausea, vomiting, and diarrhea, and fullness of the pulse, with headache.
- ▶ Chief use is to promote appetite and improve digestion in states of chronic debility.
- ▶ For atony of the stomach and bowels, with feeble or slow digestion, it is an ideal stimulating tonic; and after prolonged fevers and infections, when the forces of life are greatly depressed and recovery depends upon increased power to assimilate foods, gentian may be used to improve gastric digestion and thus hasten the convalescence.
- ▶ Gentian is especially useful in anorexia, in the dyspepsia of malarial origin, and in subacute gastritis and intestinal catarrh.

*

Gentiana Research

Br. J. Nutr. 2016 Nov 10;1-10. [Epub ahead of print]

Microencapsulated bitter compounds (from *Gentiana lutea*) reduce daily energy intakes in humans.

Mennella J¹, Fogliano V², Ferracane R¹, Aiorio M³, Pattarino F³, Vitaglione P¹.

Author information

Abstract

Mounting evidence showed that bitter-tasting compounds modulate eating behaviour through bitter taste receptors in the gastrointestinal tract. This study aimed at evaluating the influence of microencapsulated bitter compounds on human appetite and energy intakes. A microencapsulated bitter ingredient (EBI) with a core of bitter *Gentiana lutea* root extract and a coating of ethylcellulose-stearate was developed and included in a vanilla

However, a trend for a higher response of glucagon-like peptide-1 after EBIP than after CP was observed. EBIP determined a significant 30 % lower energy intake over the post-lunch period compared with CP. These findings were consistent with the tailored release of bitter-tasting compounds from EBIP along the gastrointestinal tract. This study demonstrated that microencapsulated bitter secoiridoids were effective in reducing daily energy intake in humans.

KEYWORDS: EBIP microencapsulated bitter ingredient-enriched pudding; EC endocannabinoids; EI energy intake; GI gastrointestinal; GIP glucose-dependent insulinotropic peptide; GLP-1 glucagon-like peptide-1; PP pancreatic polypeptide; PYY peptide YY; Bitter taste receptors; Microencapsulation; Nutrient sensing; Satiety

PMID: 27829482 DOI: 10.1017/S0007114516003858



Gentian Summary

- ▶ Gentian is the quintessential bitter. It is one of the most bitter substances on the planet
- ▶ Gentian has tonic effect on the entire constitution. It has the classic "sweet taste, followed by bitter taste" characteristic of many constitutional tonics (example: ginsengs)
- ▶ Gentians are found all over the planet. Every indigenous people has had access to a gentiana
- ▶ A true bitter can taste in a 1 to 30,000 dilution
- ▶ Cold and drying nature

The Green Fairy

ARTEMISIA ABSINTHIUM (WORMWOOD)



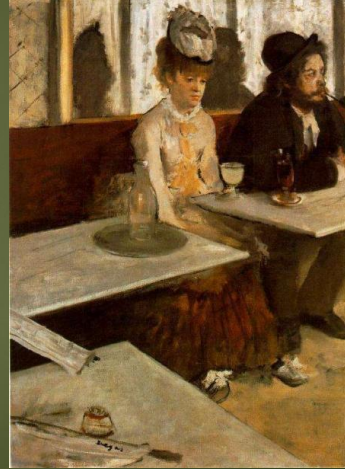
Wormwood

- ▶ Wormwood
- ▶ The Green Fairy
- ▶ la fee verte
- ▶ The Green Muse
- ▶ From Greek work "apsinthion" meaning undrinkable



Historical Uses of Wormwood

- ▶ In the Bible, grew in the Garden of Eden.
- ▶ Ebers Papyrus 1550 B.C earliest written use.
- ▶ Pliny the Elder noted its use against worms.
- ▶ John Gerald 1597 Herbal, noted gastric tonic.
- ▶ 18th century use as popular drink Absinthe.



Chemistry of Wormwood

- ▶ Volatile Oils: monoterpene alpha and beta thujone, chamazulene.
- ▶ Sesquiterpene lactones (bitters) including, absinthin and others.
- ▶ Acetylenes: In the root.
- ▶ Flavonoids: quercetin and others
- ▶ Phenolic Acids: coumaric and vanillic
- ▶ Lignans.

Traditional Clinical Uses

- ▶ Choloretic
- ▶ Anthelmintic, antiparasitic
- ▶ Stomachic, bitter
- ▶ Stimulates appetite
- ▶ Sweet smell contrasts to bitter taste.
- ▶ Bittersweet medicines use to promote balance.
- ▶ Good for integration of physical and emotional levels.
- ▶ Useful for breaking the cycle of destructive behavior.



Wormwood: Keys

- ▶ Long history of medicinal use and abuse
- ▶ Used to shift human thoughts
- ▶ Powerful nervine herb that affects consciousness
- ▶ Used to bring emotion and spiritual balance
- ▶ A bittersweet medicine



Quassia: *Quassia amara*

Quassia amara

Formaly as: *Picraena excelsa* (LINDL.)

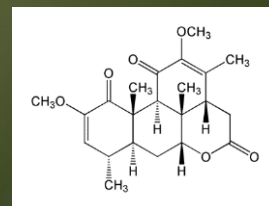
Family: N.O. Simarubaceae

- Synonyms---Bitter Wood. Jamaica Quassia. Bitter Ash. Quassia Amara (Linn.). Quassia Lignum, B.P.
Part Used---Wood of trunks and branches.
- Habitat---Jamaica.
- Quassia, also known as Jamaica Quassia and Bitter Wood, is a small, shrubby tree native to the West Indies. Its species name, *amara*, is derived from the Spanish word *amargo*, which means "bitter."
- The name fits since the bark of **the tree contains quassin, a substance 50 times more bitter than quinine**. In fact, it's the bitterest naturally-occurring chemical known to exist.



Quassia amara: Tropical bitter

- ▶ In the wood a share of 0.09 to 0.17% of quassin and 0.05 to 0.11% of neoquassin was detected in Costa Rican plants.
- ▶ Quassin is one of the most bitter substances found in nature.
- ▶ Other identified components of bitterwood are: beta-carbolines, beta-sitostenone, beta-sitosterol, dehydroquassins, gallic acid, gentisic acid,



Dandelion: Earth Nail



Taraxacum officinale

- ▶ **Family:** Asteraceae
- ▶ **Habitat:** Found throughout most of the world, particularly the Northern hemisphere
- ▶ **Collection:** The roots are best collected between June and August when they are at their most bitter. Split longitudinally before drying. The young leaves may be collected at any time, although those collected in the spring are less bitter.
- ▶ **Part Used:** Root and/or leaf
- ▶ **Taste:** Bitter, salty, sweet
- ▶ **Temperature:** Cold
- ▶ **Channels:** Liver, Gall Bladder, Spleen, Bladder



Taraxacum officinale



- ▶ **Actions:**
- ▶ Diuretic (leaf), hepatorestorative, hepatoprotective
- ▶ Choloretic, cholagogue, anti-inflammatory
- ▶ Anti-rheumatic , gentle laxative, alterative,
- ▶ Anti-hypertensive , stomachic, tonic, bitter

e

Taraxacum officinale

- ▶ Root is for liver, leaves are for kidney
- ▶ Leaves are a potassium rich diuretic. Supportive in blood pressure
- ▶ Root is a choloretic and cholagogue. Useful for liver and biliary problems of all kinds.



Taraxacum officinale

- ▶ **Preparations & Dosage:**
- ▶ Decoction: put 1-3 teaspoonful's of the root into one cup of water, decoct for 10-15 minutes.
- ▶ If using leaves, infuse rather than decoct for 10-15 minutes. This should be drunk three times a day.
- ▶ The leaves may also be eaten raw in salads or steamed as a spring green.
- ▶ Juice of the pureed leaves; sig up to 20 ml/ day
- ▶ Extract (1:5 40 % EtOH): 2.8 ml of the root and/or leaf



Cynara scolymus (Artichoke) Fruit and Leaf



Cynara scolymus (Artichoke)

- ▶ Common names: Artichoke, globe artichoke, Fruit eaten as a vegetable
- ▶ Member of the daisy (Asteraceae) family
- ▶ Pleasantly bitter taste in fruit
- ▶ Leaves extremely bitter
- ▶ Combines both liver and gallbladder action
- ▶ Well research to support liver and lipid levels



Cynara

- ▶ Anti-toxic
- ▶ Liver tonic, restorative, stimulates bile production, relieves gas, relieves cramping, relieves nausea
 - ▶ Promotes liver cell regeneration
 - ▶ Promotes blood flow to the liver
 - ▶ Stimulates bile production (Caffeoylquinic acids, e.g. Cynarin)
- ▶ Aids in metabolism of blood lipids
- ▶ Decreases cholinesterase and supports healthy liver composition.
- ▶ Classic remedy for indigestion

Cynara

Chemical constituents

- ▶ Up to 2% phenolic acids, mainly 3-caffeoylquinic acid (chlorogenic acid)
- ▶ 1,5-di-O-caffeoylquinic acid (cynarin)
- ▶ Caffeic acid
- ▶ 0–4% bitter sesquiterpene lactones of which 47–83% is cynaropicrin
- ▶ 0.1–1.0% flavonoids including glycosides
- ▶ Phytosterols (taraxasterol)
- ▶ Sugars
- ▶ Inulin
- ▶ Enzymes
- ▶ Volatile oil consisting mainly of sesquiterpenes
 - ▶ b-selinene
 - ▶ caryophyllene

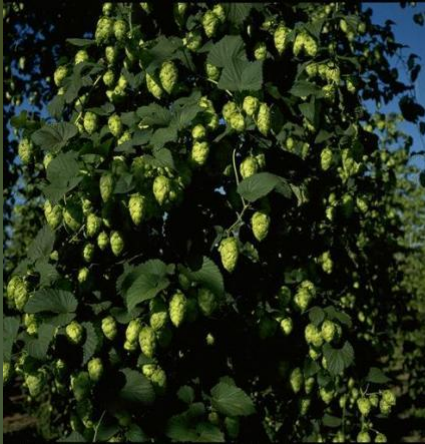


Humulus lupulus: Wolf plant



As the ancients said, hops grew "wild among willows, like a wolf among sheep," hence the name *Humulus lupulus*

Hops: Strobile



Humulus lupulus: Hops

- ▶ Family: Cannabaceae
- ▶ Same family as Cannabis
- ▶ Part Used: Female Strobiles
- ▶ The plants are unisexual (separate male and female plants).
- ▶ Both plants contain a resin that has strong physiologic properties.
- ▶ Marijuana contains THC (tetrahydrocannabinol) and Hops contains Lupulin.



Hops: Chemistry

- ▶ Volatile oil (humulene, myrcene, caryophylline, farnescene);
- ▶ 15-25 % resinous bitter principles
- ▶ Organic Acids known as alpha acids and beta acids
- ▶ estrogenic substances (Phytosterols),. 8- prenylnaringenin, 6 prenylnaringenin and isoxanthohumol
- ▶ The oil and bitter resins together are known as lupulin. Lupulin is a yellow powder. Found in the strobile



Hops: Action

- ▶ *Humulus* is stated to possess sedative, hypnotic, diuretic (like beer) and topical bactericidal properties. Phytoestrogenic.
- ▶ The German Commission E approved use for mood disturbances such as restlessness and anxiety as well as sleep disturbances. Has a high level of phytosterols. Has been used like soy and flax for hot flashes and menopausal symptoms. In men it may be a anaphrodisiac (lowers sex drive)
- ▶ Bitter agent: Stimulates digestion

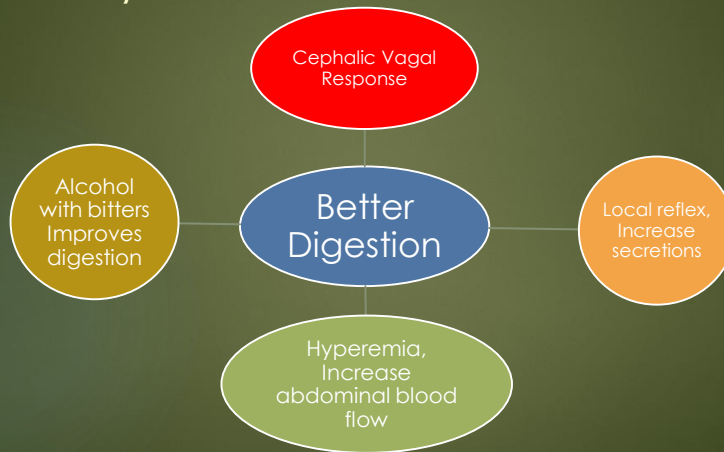
Specific Indications for Hops (Fyfe 1903)

- ▶ Nervousness, irritability, insomnia, irritation of bladder, fermentative indigestion with acid eructation's. (Lloyd Dose Book)
- ▶ Impairment of the digestive organs, resulting from abuse; exhaustion and irritability of the stomach; flatulent colic; incontinence of urine; priapism and involuntary seminal emissions; deranged conditions of the brain and nervous system. (Fyfe)

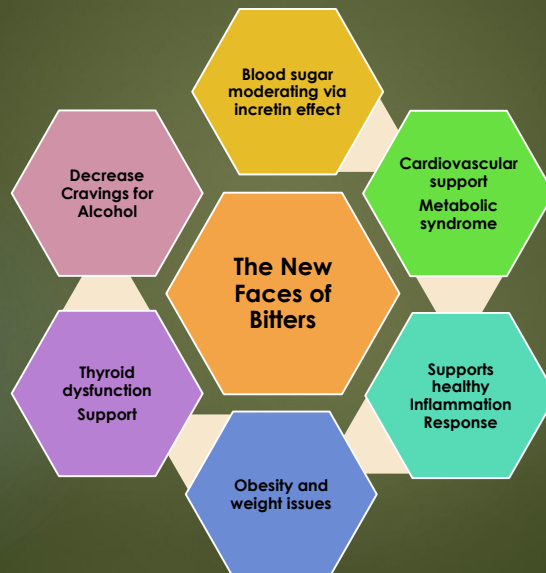
Aperitif , digestif and bitters

- ▶ **Apéritifs** and **digestifs** are drinks, typically alcoholic, that are normally served before (apéritif) or after (digestif) a meal.
- ▶ Apéritif may also refer to a snack that precedes a meal. This includes, chocolate, crackers, cheese, pâté or olives.
- ▶ "Apéritif" is a French word derived from the Latin verb *aperire*, which means "to open." The French slang word for aperitif is "apro."
- ▶ Bitters are botanical drinks that are bitter and are often used as Aperitifs or Digestifs to support digestion.

Summary: How bitters improve digestion (Traditional)



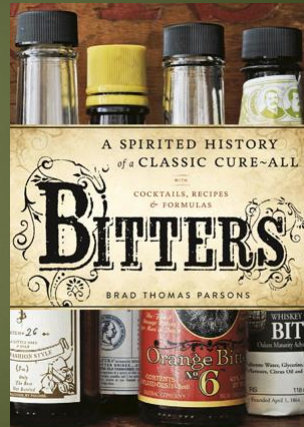
Summary: New bitter understanding



Resources for bitters

► Books

- [A Spirited History of a Classic Cure All: Bitters](#) by Brad Thomas Parsons, 2011
- [DIY Bitters: Reviving the Forgotten Flavor](#) by Jovial King and Guido Mase, 2016
- [Bitterman's Field Guide to Bitters & Amari](#) by Mark Bitterman, 2015



Thank You!

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