Good Digestive Health and Beyond: The Unfolding Story of Bitter Herbs

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Kerry Bone is the co-founder and innovation driver at MediHerb, where he serves as Director of Research and Development. In 2016 MediHerb was awarded the American Botanical Council’s (ABC’s) Varro E. Tyler Award for excellence in Phytomedicinal Research.

As part of his educational role, Kerry is Principal of the Australian College of Phytotherapy and also Adjunct Professor at New York Chiropractic College, providing input into their postgraduate applied nutrition program.

Kerry is co-author of more than 30 scientific papers on herbal research. He has also written and co-written six popular textbooks on herbal medicine, including his latest, the second edition of Principles and Practice of Phytotherapy which was awarded the 2013 James A. Duke Excellence in Botanical Literature Award by the ABC.

Kerry maintains a busy herbal and naturopathic practice in Toowoomba, Queensland, where he has been in continuous service for more than 30 years.

In 2015, Kerry’s lifelong contribution to the field of herbal medicine was recognized with his receiving the prestigious Lady Cilento award from the complementary medicine industry in Australia.
Topics Covered

- Bitter taste receptors
- Traditional view of bitters
- Bitters and digestion: modern research
- Bitters and gut hormones
Topics Covered

- Bitter receptors outside the gut: immune system, respiratory tract and more
- Insights from bitter taste variability
- Key bitter herbs and new therapeutic strategies

https://www.flickr.com/photos/blueridgekitties/14139045243
Methodology

- More than 2600 titles reviewed
- About 450 abstracts selected and read
- Around 150 full papers downloaded and read
Taste Receptors

- Two are G-protein coupled receptors (GPCRs): the TAS1Rs and TAS2Rs
- Respond to bitter, sweet and umami
- Two are ion-channel receptors: salt and sour

Pydi SP, Bhullar RP, Chelikani P. *Adv Pharmacol* 2014; **70**: 303-326. PMID: 24931200
GPCRs and Taste

- Three TAS1Rs
- TAS1R1 combined with TAS1R3 detects umami
- TAS1R2 with TAS1R3 detects sweet
- 29 human TAS2Rs detect bitter compounds

Pydi SP, Bhullar RP, Chelikani P. Adv Pharmacol 2014; 70: 303-326. PMID: 24931200
Dì Pizio A, Niv MY. Bioorg Med Chem 2015; 23(14): 4082-4091. PMID: 25934224
TAS2R Promiscuity

Promiscuous
THR > 0.2 %
(5-15 receptors)

Selective
THR < 0.05 %
(1 receptor)
THR = target hit rate

Why the Bitter Taste

- Thought to be defensive
- Many toxins are bitter
- Carnivores and birds $\Rightarrow$ fewer bitter receptors than herbivores

Hu LL, Shi P. Dongwuxue Yanjiu 2013; 34(E3): E75-E81. PMID: 23776004
Wang K, Zhao H. Genome Biol Evol 2015; 7(9): 2705-2715. PMID: 26342138
Traditional View of Bitters

- A bitter principle (compound) will powerfully stimulate gastric juice secretion
- Will also have a general tonic action
- $\uparrow$ appetite $\Rightarrow$ probably due to $\uparrow$ circulation in abdominal organs
- Effects are not just limited to the stomach

Traditional View of Bitters

- Bitters need to be tasted (registered on the taste buds on the tongue)
- Prime/prepare upper digestive function
- Reflex response via vagus nerve ⇒
  - ↑ gastric acid
  - ↑ gastrin
  - ↑ pepsin
  - ↑ pancreatic enzymes

TCM View of Bitters

- Herbs have 4 properties: cold, hot, warm and cool
- And 5 flavors: sour, bitter, sweet, pungent and salty
- Sour and bitter: attributed to yin (static, descending, cold)
- Bitter consolidates the body, eases dampness and purges heat

Ayurvedic View of Bitters

TRADITIONAL AND STATISTICAL CONCORDANCE

PLANT TASTE

PUN-GENT

SWEET

GENT

ASTRIN

SOUR

nutritive spermatopoetic tonic

digestive beneficial for throat antiinfectious

antianorexia cardioprotective antiemetic

antidiuretic antidiarrheal antidiabetic

Ethnopharmacological action

digest poisons antitoxic febrifugal

Bitter Receptors Everywhere!

- Up until the early 2000’s ⇒ bitter receptors only on the tongue
- Since then found throughout the digestive tract and elsewhere
- Main cell in gut bearing bitter receptors ⇒ enteroendocrine cell
The Gut is a Tasting Organ

Enteroendocrine Cells

- **G cells**: stomach, secrete gastrin
- **I cells**: duodenum and jejunum, secrete cholecystokinin (CCK)
- **K cells**: duodenum, secrete gastric inhibitory peptide (GIP)
- **L cells**: duodenum, jejunum and colon (mainly), secrete glucagon-like peptide (GLP-1) and protein YY (PYY)

Gribble FM. *Proc Nutr Soc* 2012; **71**(4): 456-462. PMID: 22906726
Brainstem Y2 and GLP-1Rs accessible to circulating hormone may mediate direct central effects of PYY and GLP-1.

Central hypothalamic pathways controlling energy homeostasis may be modulated directly or indirectly by PYY and GLP-1.

PYY and GLP-1 released from L-cells into the circulation.

Y1 and GLP-1Rs on pancreatic β-cells may mediate direct effects on insulin release.

GLP-1/PYY signalling via the vagus.

Ileal brake

Spreckley E, Murphy KG. Front Nutr 2015: 23. PMID: 26258126
Bitter Receptors and Digestion: The Research

- Hop beer bitter acids $\uparrow \uparrow$ gastric acid in vitro $\Rightarrow$ gustducin/gastrin?\(^1\)
- Activation of bitter receptors $\Rightarrow$ $\uparrow$ CCK and PYY in vitro\(^2,3\)
- Bitter agonists in gut activate neurons in brain $\Rightarrow$ mediated by CCK and PYY\(^2\)

Bitter Receptors and Digestion: The Research

- Bitter taste receptors and $\alpha$-gustducin $\Rightarrow$ ↑ ghrelin and ↓ gastric emptying in vivo$^1$
- Strong bitter tastants induced marked nausea in 20% of 63 people (another 45% mild to moderately nauseated)$^2$
- Bitter-induced anion (chloride, bicarbonate) secretory activity observed in human colonic cells in vitro$^3$

Bitters and Appetite/Hunger

- A series of tests in healthy people
- Intragastric introduction of synthetic bitter (denatonium benzoate)
- ↓ hunger and ↑ satiation

Bitters and Appetite/Hunger

- Quinine hydrochloride (18 mg, enteric-coated)
- 60 minutes before eating
- Calorie intake ↓ 14% (p=0.007)
- CCK increased at 90 minutes (p=0.026)
- Crossover RCT in 20 healthy people

Definition of Incretins

“Gut derived factors that increase glucose-stimulated insulin secretion”

Intestine Secretion Insulin

Incretin Hormones

- Produced by gastrointestinal tract in response to incoming nutrients
- Stimulate insulin secretion
- Incretin hormones:
  - Glucagon-like peptide 1 (GLP-1)
  - Gastric inhibitory polypeptide (GIP)

Bitter Herbs Stimulate GLP-1

- Berberine via TAS2R38 in vitro\(^1\)
- Gentian (\textit{Gentiana scabra}) in vitro and in vivo\(^2\)
- Bitter Melon (\textit{Momordica charantia}) via its bitter triterpenoid glycosides in vitro\(^3\)

Bitters Regulate Metabolic Function

Insulin resistance

- 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 \(^1\)

Bitter Receptors Everywhere!

- Thymus\(^1\)
- Kidney\(^2\)
- Epidermis\(^3\)
- Thyroid\(^4\)
- Vascular smooth muscle\(^5\)
- Heart\(^6\)

- Urinary tract\(^7\)
- Bone marrow\(^8\)
- Immune cells\(^9\)
- Testes\(^10\)
- Olfactory cells\(^11\)
- Lungs\(^12\)
References from Previous slide

Bitter Receptors & The Immune System

P. aeruginosa

Acylhomoserine lactones

AHL

T2R38

NO

Nitric oxide

AVI allele

PAV allele

Ca²⁺

Cytoplasm

Bitter Receptors & The Immune System

- Experimental studies ⇒ bitter response ↑ by tumor necrosis factor (TNF)¹

- Many immune cells possess bitter taste receptors²

- Part of the innate immune response³

Bitter Receptors & The Immune System

- Bitter tastants ↓ IgE-dependent mast cell activation (anti-allergic)
- Especially TAS2Rs 3,4,10,14 and 46
- Amarogentin (from Gentian) ↓ histamine and TNFα from human mast cells

Bitter Receptors in Airways
Functions of TAS2Rs in lungs

Epithelium/Chemosensory cells
- Antimicrobial peptide secretion/airway reflexes

Sensory nerve fibers

Epithelium/Ciliated cells
- Ciliary beat frequency

Smooth muscle
- Relaxation

Pulmonary artery
- Contraction/relaxation

Macrophage
- Cytokine release

Mast cell
- Histamine and PGD$_2$ release

Bitter Taste Variability

- Chemist Arthur Fox in 1931 accidentally spilled phenylthiocarbamide (PTC)
- A colleague complained of bitter taste of dust, but Fox could not taste\(^1\)
- Found to have a genetic basis in 1932\(^2\)

1. Fox AL. *Proc Natl Acad Sci USA* 1932; 18(1): 115-120. PMID:16577421
2. Blakeslee AF. *Proc Natl Acad Sci USA* 1932; 18(1): 120-130. PMID: 16577422
Bitter Taste Variability

- Now tend to use related compound propylthiouracil (PROP)
- Have 3 different PROP phenotypes: supertasters (approx 30%), medium tasters (approx 40%), non-tasters (approx 30%)\(^1,2\)
- In 2003/4 discovered to be linked to TAS2R38 single nucleotide polymorphisms (SNPs)\(^3,4\)

Bitter Taste Variability
Genotype/phenotype is complex

TAS2R38 VARIANTS

GUSTIN
(salivary trophic factor)

SPECIFIC bPRPs
SALIVARY PROTEINS

OTHER BITTER RECEPTORS

PROP SENSITIVITY PHENOTYPE

TAS2R38 EXPRESSION

Tepper BJ, Banni S, Melis M et al. *Nutrients* 2014; 6(9): 3363-3381. PMID: 25466026
Genetics of Taste

- TASR38 most studied because is bitter receptor for PTC and PROP
- However, other SNPs at other bitter receptors give bitter taste/response variability
- Most common TAS2R38 haplotype SNPs are:
  - PAV (dominant, taster status)
  - AVI (recessive, non-taster status)

Genotype Versus Phenotype

- Study in 51 healthy people
- PROP taster status versus TAS2R38 genotype
- For the latter, genetically:
  - 10 (20%) PAV/PAV
  - 23 (45%) PAV/AVI
  - 18 (35%) AVI/AVI

Genotype Versus Phenotype

- 100% of AVI/AVI were non-tasters
- 70% of PAV/PAV were supertasters (rest were medium tasters)
- For PAV/AVI ⇒
  - 22% supertasters
  - 74% medium tasters
  - 4% non-tasters

Taster Status Versus Health

- Two types of studies:
  - phenotypic (PROP, PTC tester status)
  - genotypic (TAS2R38 SNPs)

- Various health outcomes assessed:
  - BMI/obesity
  - Smoking
  - Motion sickness
  - Eating habits
  - Dental caries
  - Alcohol intake
  - Metabolic syndrome
  - Diabetes risk
Taster Status and Smoking

- PAV negatively linked and AVI positively linked to smoking quantity\(^1\)
- Carriers of at least one PAV allele: lower cigarette intake/day\(^2\)
- TAS2R expression on tongues of smokers lower than non-smokers (less than 20%)\(^3\)

Taster Status and Dental Caries

- Several studies ⇒ PROP non-tasters ↑ caries and *Streptococcus mutans* in primary dentition and teens ¹,²,³

- PAV haplotype ⇒ protection against caries⁴

- In vitro study ⇒ PAV haplotype: substantially higher innate immune response to *S.mutans⁵*

Taster Status and Rhinosinusitis

- 2013 review
- Of patients with gram-negative or *Pseudomonas aeruginosa* growth: none had PAV/PAV TAS2R38 genotype
- PAV/PAV genotype far less likely to require sinus surgery. Longer follow-up study ⇒ confirmed

Taster Status and Rhinosinusitis

- PTC supertasters $\Rightarrow$ less frequent sinus infection\(^1\)

- After sinus surgery: symptomatic improvement in 22-item Sino-Nasal Outcome Test (SNOT-22):
  - PAV/PAV 38 points
  - PAV/AVI and AVI/AVI only 12 points\(^2\)

Bitters and Physical Performance

- Mouth rinsing and ingesting quinine solution significantly improves mean and peak output in maximal 30 second cycling sprint

- But tasting and not ingesting did not

- Observed ↑ corticomotor excitability suggested as mechanism

The Broad Spectrum of TAS2Rs

- Clinical study: 34 volunteers exposed to 8 bitter compounds (including PROP and PTC)
- Each participant displayed a unique tasting profile
- PROP taster status NOT correlated with taster status for the other compounds

Key Herbal Bitter Compounds

- Amarogentin from Gentian stimulates seven receptors: TAS2R1, 4, 39, 43, 46, 47 and 50
- Absinthin from Wormwood stimulates four: TAS2R10, 14, 46 and 47
- Parthenolide from Feverfew stimulates seven: TAS2R1, 3, 8, 10, 14, 44 and 46
- Quinine activates nine receptors

## Key Herbal Bitter Compounds

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<tr>
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<th>TAS2Rs</th>
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<tr>
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<tr>
<td>Amaro gentin from Gentian</td>
<td>✓</td>
</tr>
<tr>
<td>Absinthin from Wormwood</td>
<td></td>
</tr>
<tr>
<td>Parthenolide from Feverfew</td>
<td>✓</td>
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Gentian, Wormwood & Feverfew together,
Activate 12 out of 29 bitter receptors
Gentian

- *Gentiana lutea* contains some of the most bitter chemicals known, including amarogentin
- Clinical trial liquid (tasted): ↑ saliva, ↑ gastric secretion, ↑ bile release and production
- Clinical trial capsule (not tasted): relief of symptoms of constipation, flatulence, appetite loss, vomiting, heartburn, abdominal pain, nausea

**Wormwood**

- *Artemisia absinthium* contains the intensely bitter compounds absinthin and artabsinthin.

- Liquid (tasted): ↑ gastric secretion in a clinical trial.

- Another trial liquid ↑↑↑↑ duodenal levels of pancreatic enzymes and bile.

- Also clinically beneficial in Crohn’s disease (capsule).


Krebs S, Omer TN, Omer B. *Phytomedicine* 2010; **17**(5): 305-309. PMID: 19962291
Combining Bitters

- Are energetically cold
- Hence best to combine with warming, aromatic herbs such as Ginger and Chen Pi
- Use several bitters together to overcome less reactive SNPs
- For extra effect on bile output: combine with cholagogue and choleretic herbs eg Globe Artichoke and Dandelion Root
Closing Remarks

- The true value of bitters has been rediscovered
- Bitter receptors function not just on the tongue, but in the rest of the gut and beyond
- Bitter receptors in the gut regulate digestion, blood sugar, laxation and satiety
Closing Remarks

- Blending bitters together will have more clinical impact $\Rightarrow$ wider range of bitter receptors impacted

- Corollary is best bitter herbs will impact the larger number of receptors
Closing Remarks

- Modern findings also support the role of bitter herbs in:
  - Insulin resistance
  - Metabolic syndrome
  - Type 2 diabetes
  - and perhaps even weight loss and depression (based on the known activities of CCK and GLP-1)
Closing Remarks

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

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https://www.flickr.com/photos/johnsu01/3286038831
Acknowledgment

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Thank You and Questions