Field Applications of Botanical Medicine: Bitters, Digestives and Aperitif’s

Bitter herbs have a long history of being used as a stimulating digestive aid. In this class, we will focus on the rebirth of bitters, and work to create several delicious modern bitters.

Glen Nagel, ND
2 hours General CE
July 13th 2016
Bitter Learning Objectives

• The physiology of bitters in nature and the clinical indications
• An Overview of clinical indications for bitters and digestive health.
• Overview of contraindication and toxicology of bitter medicine.
• Discussion of true bitters and aromatic bitters, review of material medica of the various types
• Identification and clinical use of bitters: Artemisia absinthium, Humulus lupulus, Achillea millefolium, Boneset
Digestive Problems are Big Health Concerns
## Top 20 Prescription Drug Sales 2014

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Indications</th>
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<tbody>
<tr>
<td>1</td>
<td>Abilify</td>
<td>Depression, bipolar disorder, schizophrenia</td>
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<tr>
<td>2</td>
<td>Humira</td>
<td>Rheumatoid arthritis, psoriatic arthritis</td>
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<td>3</td>
<td>Nexium</td>
<td>Acid reflux</td>
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<td>4</td>
<td>Crestor</td>
<td>Lowering cholesterol</td>
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<tr>
<td>5</td>
<td>Enbrel</td>
<td>Rheumatoid arthritis, psoriatic arthritis</td>
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<tr>
<td>6</td>
<td>Advair Diskus</td>
<td>Asthma (4 ya plus)</td>
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<td>7</td>
<td>Sovaldi</td>
<td>Chronic hepatitis C (CHC) infection</td>
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<td>8</td>
<td>Remicade</td>
<td>Ankylosing spondylitis, psoriatic arthritis, Crohn's disease</td>
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<td>9</td>
<td>Lantus Solostar</td>
<td>Long-acting insulin for type 2 diabetes</td>
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<tr>
<td>10</td>
<td>Neulasta</td>
<td>Neutropenia (considered a Cancer Rx)</td>
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<tr>
<td>11</td>
<td>Copaxone</td>
<td>Multiple sclerosis (MS)</td>
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<td>12</td>
<td>Rituxan</td>
<td>Non-Hodgkin’s lymphoma</td>
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<tr>
<td>13</td>
<td>Spiriva Handihaler</td>
<td>Chronic obstructive pulmonary disease (COPD)</td>
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<td>14</td>
<td>Januvia</td>
<td>Type 2 diabetes</td>
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<tr>
<td>15</td>
<td>Lantus</td>
<td>Long-acting insulin for type 2 diabetes</td>
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<tr>
<td>16</td>
<td>Atripla</td>
<td>HIV-1 infection (AIDS)</td>
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<tr>
<td>17</td>
<td>Cymbalta</td>
<td>Major depressive disorder, GAD (general anxiety disorder), fibromyalgia</td>
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<tr>
<td>18</td>
<td>Avastin</td>
<td>Metastatic colorectal cancer (mCRC), Advanced nonsquamous non–small cell lung cancer (NSCLC), Metastatic kidney cancer (mRCC)</td>
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<tr>
<td>19</td>
<td>Lyrica</td>
<td>Neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, fibromyalgia</td>
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<tr>
<td>20</td>
<td>Oxycontin</td>
<td>Chronic and severe pain</td>
</tr>
</tbody>
</table>
The Five Basic Tastes

- Sweet (Sugar, Chocolate, etc.)
- Salty (Salt, etc.)
- Umami (Soup Stock of Konbu and Bonito etc.)
- Sour (Vinegar, Lemon, etc.)
- Bitter (Coffee, Bitter Gourd, etc.)
Many types of Taste receptors

<table>
<thead>
<tr>
<th>Mammalian taste receptors and cells</th>
<th>Umami</th>
<th>Sweet</th>
<th>Bitter</th>
<th>Sodium</th>
<th>Sour and carbonation cells</th>
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<tbody>
<tr>
<td>T1R1+T1R3</td>
<td>L-glutamate</td>
<td></td>
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<tr>
<td>L-amino acids</td>
<td>L-cysteine</td>
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<td>glycine</td>
<td>L-AP4</td>
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<tr>
<td><strong>Nucleotide enhancers</strong></td>
<td>IMP, GMP, AMP</td>
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<tr>
<td>T1R2+T1R3</td>
<td>Sugars</td>
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<tr>
<td>Saccharin</td>
<td>T2R15</td>
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<td>Acesulfame K</td>
<td>T2R8, T2R4</td>
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<td>aspartame, cyclamate</td>
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<td>D-amino acids</td>
<td>T2R16</td>
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<td>D-alanine, D-serine, D-phenylalanine</td>
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<td>Glycine</td>
<td>T2R38</td>
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<tr>
<td>Sweet proteins</td>
<td>T2R43, T2R44</td>
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<td>Monellin, thaumatin</td>
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<td>~30 T2Rs</td>
<td>Cycloheximide</td>
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<tr>
<td>(mT2R5)</td>
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<tr>
<td>Denatonium</td>
<td>(hT2R16)</td>
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<td>Salcin</td>
<td>(hT2R38)</td>
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<td>PTC</td>
<td>(hT2R44)</td>
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<td>Saccharin</td>
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<td>Quinine</td>
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<td>strychnine</td>
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<td>atropine</td>
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<td>ENaC</td>
<td>Low NaCl</td>
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<td>Sodium salts</td>
<td>(hT2R48)</td>
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<tr>
<td>PKD2L1</td>
<td>Acids</td>
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<tr>
<td>Carbonated drinks</td>
<td>Citric acid</td>
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<tr>
<td>(hT2R49)</td>
<td>Tartaric acid</td>
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<tr>
<td>HCl</td>
<td>(hT2R44)</td>
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**Diagram:**
- **Umami**
  - T1R1+T1R3: L-glutamate, L-amino acids, glycine, L-AP4
  - **Nucleotide enhancers**: IMP, GMP, AMP
- **Sweet**
  - T1R2+T1R3: sugars, saccharin, acesulfame K, aspartame, cyclamate, D-amino acids, D-alanine, D-serine, D-phenylalanine, glycine, sweet proteins: monellin, thaumatin
- **Bitter**
  - ~30 T2Rs: cycloheximide, denatonium, salcin, PTC, saccharin, quinine, strychnine, atropine
- **Sodium**
  - ENaC: low NaCl, sodium salts
- **Sour and carbonation cells**
  - PKD2L1: acids, citric acid, tartaric acid, HCl
  - **CA IV**: carbonated drinks
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 3 types of Sweet receptors

• The TAS2R proteins function as bitter taste receptors. There are 43 human $TAS2R$ genes

• The standard bitter, sweet, or umami taste receptor is a G protein-coupled receptor with seven transmembrane domains. Ligand binding at the taste receptors activate second messenger cascades to depolarize the taste cell.

• Gustducin is the most common taste $G\alpha$ subunit, having a major role in $TAS2R$ bitter taste reception.
Bitter receptors found all over the body

- Old thought that they were on the back of the tongue only
- Now we know they are found all over the digestive tract
- Recent research has found them in the lungs, and bronchi
- In the placenta and thyroid gland
- Bitters receptors seem to be important!
Herbal Bitters: A long history

• 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

- 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.

- Dick’s Encyclopedia of Practical Receipts and Processes (1872)
Old Saying about Bitters

- Sweet to the taste buds, bitter to the stomach
- Bitter to the tongue, then sweet to the stomach
- Bitters are a tonic for all digestion and especially promote acid secretion
Current Concepts of how Bitters Improve Digestion

Better Digestion

Cephalic Vagal Response

Alcohol with bitters improves digestion

Hyperemia, Increase abdominal blood flow

Local reflex, Increase secretions
THE BITTER REFLEX AND ITS 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.
How Bitter Works

- Taste buds are distributed in distinct fields in the oral, pharyngeal, and laryngeal epithelia, with each field innervated by a different cranial nerve branch.
- Only the taste buds on the tongue are depicted in the figure. 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 subserve various functions, such as motor and physiological reflexes, discriminative perception, and affective processing.
New Bitter concept

• 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 *
• Bitters stimulate natural incretins and hence stimulate insulin and lower glucose *
• Bitters may act directly as endocrine triggers, by passing the CNS *
• Stimulate Hyperemia increasing GI blood flow*
• Bitter may lead to less obesity and improve metabolic syndrome via increase fullness, and hormone stimulation*

* These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease
The Bitter Truth: Its 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.*

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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.

• Bitters stimulate natural incretins and hence stimulate insulin and lower glucose *

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Types of Herbal Bitters

• **True Bitters: Only bitter**
  - Centaurium umbellatum
  - Gentiana lutea
  - Hydrastis canadensis
  - Mahonia aquifolium
  - Aloe spp. Bitter Aloe

• **Aromatic Bitters: bitter with flavor**
  - Artemisia absinthium
  - Achillea millefolium
  - Humulus lupulus

• **Nutritional bitters with Probiotics**
  - Taraxacum
  - Articum
  - Inula
  - Angelica
  - Cynara

• **Quassia bark**

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*Note: The above list is not exhaustive and additional herbal bitters may exist.*
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 of white tongue coating
- Atonic digestion and elimination
- Depression and or mood disorders *
- Digestive issues that come with aging.

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New Actions for Bitters

- Blood sugar Support *
  - Incretin effect
  - Probiotics from bitter herbs
- Cardiovascular effects *
  - Lipid Moderating
  - Metabolic syndrome
- Thyroid Balance
  - 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 *
- Bitters can down regulate Tumor Necrosis factor receptors *

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Bitters can influence all phases of Digestion

- Cephalic, Taste
- Gastric
- Intestinal

![Diagram of digestive phases](https://example.com/diagram.png)

**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
Bitters in Formulation

• 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 tincture
- Capsule and tablet of bitters have been found to be useful for GI tract bitter receptors and general systemic effects
Take the 30 day Bitter Challenge!

- To improve your digestion and overall health take the 30 day bitter challenge.
- Find a bitter formula, herb or combination that has one of the true bitters or Eupeptic Bitters.
- Take 10-30 drops of the bitter before meals, ideally 10 minutes, or after meals
- Take enough to get strong bitter sensation and “bitter shutter”
- Continue for 30 days, moving the dose up or down depending on reaction
- Assess your health before or after.