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Bitter Herbs: Improve Digestive Function & Potentially More

Key Points at a Glance

Taste Receptor Research: New Understanding & Potential Applications for Bitter Herbs

- bitter taste receptors (TAS2Rs), such as those in the taste buds detect bitter substances
- these receptors are found in tissues other than the oral cavity, including the colon and intestinal endocrine cells
- 29 functional human TAS2Rs identified to date
- some herbal bitter substances stimulate taste receptors *in vitro*
- glucagon-like peptide-1 (GLP-1) is secreted from enteroendocrine cells and augments the release of insulin from pancreatic beta-cells; cholecystokinin (CCK) is secreted by enteroendocrine cells with a range of beneficial effects on digestion, satiety, glucose homeostasis
  - herbal substances found to stimulate GLP-1 and CCK secretion from human enteroendocrine cells possibly via activation of taste receptors
- genetic variability occurs for human TAS2R genes, which for example, may result in reduced bitter taste perception
- epidemiological studies have not found a clear association for glucose dysregulation or the effect on satiety and body weight, but reduced functioning of taste receptors is associated with increased alcohol intake and reduced longevity
- clinical studies with healthy volunteers found bitter substances (quinine or denatonium benzoate) administered into the stomach or duodenum (without tasting by the mouth), reduced hunger and improved satiation, but a conflicting effect on food intake and no effect on gastric emptying
- clinical study with herbal bitter substance, administered by capsule (i.e. not tasted) had some beneficial effects in prediabetes

The Classic View of Bitters

- bitter-tasting herbs: long tradition of use, exemplified culturally by the aperitif
- in addition to appetite and digestive functions, regarded as general tonic and for fatigue
- mechanisms debated: digestive stimulation via oral taste buds, nerve involvement (reflex or direct), direct interaction with gastrointestinal tissue or a combination thereof
- thought action of bitters required they be tasted; for direct effect on gastric mucosa higher than traditional doses needed

Gentian & Wormwood

- well-known classic bitters, used for dyspepsia, poor appetite and to support recovery in debility and after infections
- contain substances that stimulate TAS2Rs *in vitro*
- preliminary tests confirm stimulating effect on digestive enzymes and bile
- clinical study found gentian improved symptoms of dyspepsia (administered by capsule i.e. not tasted; high dose)

Ginger & Chen Pi (Tangerine)

- traditional actions on GI tract: carminative, digestive stimulant; used to improve appetite and digestion
- chen pi may contain a substance that stimulates a TAS2R *in vitro*

Feverfew

- less-documented but traditional bitter; used to improve appetite and digestion
- contains a substance that stimulates TAS2Rs *in vitro*

Indications & Safety

- Poor appetite, sluggish digestion, dyspepsia, flatulence.
- As a digestive and tonic during convalescence.
- Food intolerances and allergies.
- As part of a regimen: to improve nutrient absorption and regain healthy bowel flora; possibly to support glucose homeostasis (may require high doses) and weight loss.
- Contraindicated in pregnancy, lactation and known allergy. Caution in stomach ulcer, inflammation or hyperacidity. May be appropriate to pause intake after 4 weeks (due to Wormwood).

Taste Receptor Research Suggests New Understanding of Bitter Herbs

Humans are able to distinguish between five primary tastes: bitter, sweet, sour, salty and umami. (Umami is a savoury taste caused by the presence of monosodium glutamate.) As many naturally-occurring bitter compounds are toxic, the ability to perceive bitter taste may have served as a warning against the ingestion of toxic compounds in food, although the correlation between bitterness and toxicity can vary, and some bitter substances are beneficial to health.[1-3]

The perception of bitter taste starts with the binding of specific molecules to certain receptors encoded by the taste receptor type 2 family (TAS2R) of taste receptor genes. TAS2 receptors are expressed at the surface of taste receptor cells, such as in taste buds on the tongue surface.[1,2]

Research in rats and/or mice conducted in the early 2000s discovered that there are bitter receptors in tissues other than the oral cavity including the stomach and duodenum, respiratory tract and brain.[4] It has been confirmed from research using isolated tissues and cell lines that TAS2 receptors are expressed in the human colon and intestinal endocrine cells. Of the 25 TAS2Rs in the human genome identified at the time, 17 were detected in colonic tissue.[5] This raised the possibility that taste receptors may have functions other than taste perception.2 The Gene Expression Omnibus, a public genomics data repository available online via the US National Library of Medicine (http://www.ncbi.nlm.nih.gov/geo), indicates that TAS2Rs are expressed in human tissues other than the gastrointestinal tract: including brain, heart, skeletal muscle, endometrium, liver and omental adipose tissue.[6]

As of 2010, bitter compounds had been identified as agonists (i.e. stimulating the receptor) for 20 of the 25 functional human TAS2Rs. Some TAS2Rs respond to several bitter compounds and some bitter compounds can activate several receptors. Key herbal bitter substances found to stimulate human TAS2Rs are outlined in Table 1.[7-9] Stimulation was assessed using *in vitro* calcium imaging analysis. (If and when the receptor is activated by the substance, calcium ions are released from intracellular stores and induce neurotransmitter release.) Of the 104 natural and synthetic substances tested, some compounds only produced a partial response, and two compounds (naringin from grapefruit and sulforaphane from broccoli sprouts) were inactive. In some cases, a range of concentrations were required to activate the receptors e.g. absinthin: 0.1 µM for TAS2R47, 100 µM for TAS2R10 and TAS2R14; amarogentin: 3 µM for TAS2R47, 300 µM for TAS2R4 and TAS2R39. (Note: The higher the concentration the lower the potency.)[7] Since the publication of this research, an additional four TAS2Rs have been identified, and several have been renamed (e.g. TAS2R44 and TAS2R47 are now TAS2R31 and TAS2R30, respectively) making a total of 29 functional human TAS2Rs.[10,11]

Effects in Enteroendocrine Cells

In response to food ingestion, enteroendocrine cells in the intestinal mucosa release hormones that can stimulate insulin secretion from the pancreas thereby reducing blood glucose. This is known as the incretin effect and two hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), have been identified as the incretins.[18] The predominant role of GIP seems to be related to increased adipogenesis, while GLP-1 is an important regulator of glucose homeostasis, as well as regulating appetite and gut motility.[19,20] Increasing

Compound	Herb‡	Bitter Taste Receptor (TAS2R)§	Ref
absinthin	wormwood herb (*Artemisia absinthium*)	10, 14, 46, 47	7
aloin	aloe resin (*Aloe barbadensis*)	43	7
amarogentin	gentian root (*Gentiana lutea*)	1, 4, 39, 43, 46, 47, 50	7
andrographolide	*Andrographis paniculata* leaves	46, 47, 50	7
arbutin	bearberry leaves (*Arctostaphylos uva-ursi*)	16	7
cynaropicrin	globe artichoke leaf (*Cynara scolymus*)	46	8
green tea catechins	green tea leaves (*Camellia sinensis*)	39	9
grosheimin	globe artichoke leaf (*Cynara scolymus*)†	43, 46	7
humulone isomers	hops strobiles (*Humulus lupulus*)	1, 14, 40	7
limonin	*Phellodendron amurense* bark and possibly chen pi (*Citrus reticulata*) peel^	38	7
marrubiin	*Marrubium vulgare* leaves	46	8
parthenolide	feverfew leaves (*Tanacetum parthenium*)	1, 4, 8, 10, 14, 44, 46	7
salicin	willow bark (*Salix* spp.)	16	7
sinigrin	horseradish root (*Armoracia rusticana*)	16, 38	7
alpha-thujone	essential oils of *Thuja occidentalis* leaf and wormwood (*Artemisia absinthium*) leaf and flowering tops*	10, 14	7

Table 1. Substances from common medicinal plants found to stimulate human TAS2 receptors *in vitro*.

Note: ‡ Present as a major or characteristic constituent, or minor constituent present in more than trace amounts. § Present in colonic tissue: TAS2R3, 4, 5, 10, 13, 38, 39, 40, 42, 43, 44, 45, 46, 47, 49, 50, 60; present in intestinal endocrine cell lines: TAS2R4, 5, 13, 14, 16, 38, 39, 40, 44, 46, 47, 49, 50, 60;[5] – nomenclature prior to the 2015 renaming. † Present in much smaller amounts than cynaropicrin.[12] ^ Amount varies depending on variety and stage of maturation of fruit.[13-15] * Amount can vary substantially in wormwood essential oil from relatively high to very low/almost absent, and depends on growing conditions and chemotype.[16,17]

research has focussed on the role of GLP-1 in type 2 diabetes and weight loss: the use of GLP-1 analogues and inhibitors of dipeptidylpepidase 4 (DPP-4, the enzyme that breaks down both GLP-1 and GIP).[18,19] A major adverse effect of GLP-1 analogue treatments is nausea, an effect that is not seen with DPP-4 inhibitors.[19] Other means of increasing GLP-1 secretion, such as via stimulation of bitter receptors, may provide an alternative or supporting strategy in type 2 diabetes.

Calcium imaging analysis can only be used for compounds that cause calcium signalling as a consequence of receptor activation.[11] Using a different *in vitro* model, berberine was found to stimulate glucagon-like peptide (GLP)-1 secretion from human enteroendocrine cells via activation of TAS2R38. (GLP-1 is secreted from enteroendocrine cells and augments the release of insulin from pancreatic beta-cells.)[21] Berberine, in doses around 1000 mg/day, which is higher than is found naturally in herbs such as golden seal (*Hydrastis canadensis*), has demonstrated hypoglycaemic activity in diabetics,[22,23] and secretion of GLP-1 by berberine was considered one of many possible mechanisms (investigated using *in vitro* and *in vivo* animal models).[21] These are the first results to suggest this mechanism may involve berberine acting as a taste receptor agonist in intestinal cells. The experimental model was rigorous, using human enteroendocrine cells and antibodies of TAS2R38.

The possible role of GLP-1 via activation of bitter taste receptors in the hypoglycaemic effects of bitter gourd (*Momordica charantia*) has also been investigated, although using a less rigorous *in vitro* model. Water extract of bitter gourd fruit and seeds stimulated GLP-1 secretion in enteroendocrine cells obtained from mice. Several fractions of the extract were tested. The highest stimulation was produced by the fraction rich in the bitter-tasting triterpenoid glycosides, momordicoside K and momordicoside L. The stimulations were partially inhibited by probenecid, an inhibitor of human TAS2R16, and by U-73122, a phospholipase Cβ2 inhibitor. (Phospholipase Cβ2 (PLCβ2) is a key enzyme in mammalian taste signal transduction.) The results suggest that the GLP-1 stimulation might involve, at least in part, bitter taste receptors and/or the PLCβ2-signaling pathway. Further investigation is needed using a human bitter taste receptor model.[18]

Cholecystokinin (CCK) is a peptide secreted by the upper intestinal mucosa, specifically the enteroendocrine cells, and is also found in the central nervous system. It stimulates release of pancreatic exocrine (or digestive) enzymes, causes gallbladder contraction and affects other gastrointestinal functions (such as inhibiting gastric emptying and food intake). CCK may be the mediator of satiety.[24] Enteroendocrine cells are in close contact with the intestinal lumen and are considered to act as mucosal taste cells by, for example, sensing compounds in the luminal content.[25] Stimulation of bitter receptors in enteroendocrine cells which promotes the release of peptides, in particular CCK, may lead to a range of beneficial effects on digestion, satiety and glucose homeostasis.[26]

Bitter substances were found to stimulate the release of CCK from enteroendocrine cells of mice (*in vitro*).[27] One hypothesis suggested that TAS2 receptors in the intestinal tract may stimulate the secretion of gut peptides, such as CCK, to limit the absorption of potentially toxic compounds that reach the small intestine.[28,29]

The bitter tasting succulent stem of *Hoodia gordonii* contains a mixture of steroid glycosides that have demonstrated appetite-suppressing effects in animals and humans. One of the steroid glycosides induced secretion of CCK in rat intestine *ex vivo* and in human enteroendocrine cells *in vitro*. The steroid glycoside stimulated TAS2R7 and TAS2R14 (this was observed using calcium imaging.) As TAS2R14 is expressed in the particular human enteroendocrine cell used in the experiment and also in human proximal intestinal tissues (duodenum and jejunum), this provides preliminary evidence that CCK secretion is mediated via TAS2R14.[30]

Epidemiological and Clinical Trial Data

Genetic variability has been observed for a number of human TAS2R genes, including single nucleotide polymorphisms (SNPs). As of 2011 variations in TAS2R16, TAS2R38, TAS2R43 and TAS2R44 have been associated with differential bitter taste perception. Three SNPs in the TAS2R38 gene are largely, but not completely,[31,32] responsible for the differences in tasting the bitterness of the synthetic compounds phenylthiocarbamide (PTC) and propylthiouracil (PROP).[33] The TAS2R38 haplotypes show a range of responses from low to high sensitivity. The dominant haplotype (PAV) usually has high sensitivity, and AVI homozygotes do not have the ability to taste PROP. Other haplotypes have intermediate sensitivity.[34] However, it has been observed in some volunteers that AVI homozygotes have responded strongly to PROP and those with PAV have responded very little, which strongly suggests that there are genetic and environmental factors other than TAS2R38 involved.[35]

- An association was found between glucose and insulin dysregulation in non-diabetic individuals and three SNPs. The SNPs were associated with TAS2R7 and TAS2R9. It was concluded that the TAS2R9 variant was the most likely to alter the receptor function. At the time, no compounds were known to activate this receptor, so the researchers screened 64 bitter-tasting compounds, and found three drugs able to stimulate TAS2R9 in isolated cells. Even high concentrations of these bitter stimulants were unable to elicit responses in cells containing the variant of TAS2R9. The gene

study also found increased incidence of type 2 diabetes, with significant associations found for several SNPs, the strongest with the TAS2R7 gene.[36]

- In a cross-sectional study, a marginally lower risk of diabetes was observed among those with the nontaster TAS2R38 haplotype than among those with the taster haplotype (odds ratio: 0.69; 95% CI: 0.48, 1.00).[37]
- In non-diabetic men a relationship was observed between genetic variants of TAS2R38 and 30-minute plasma glucose levels as well as area under the curve (AUC) of plasma glucose. Minor allele carriers had increased levels of these parameters. There was no association found in women, or for other markers of glucose or insulin metabolism. In addition, significantly increased 30-minute plasma glucose levels and AUC values were observed in male and female AVI allele carriers compared to PAV allele carriers. PROP tasting sensitivity was not tested in this cohort.[38]
- The association between PROP taster status and body mass index (BMI) or obesity has often been investigated but with contradictory results. It is likely that other factors play a role.[39-42] Few of the studies examined the effects of both TAS2R38 and PROP taster status on food intakes. (Although PROP taster status is linked to TAS2R38 genotype, both can separately influence food preferences, and by extension, energy intake and body weight.) In two studies that have investigated both factors, phenotype (PROP taster status) was more influential than TAS2R38 genotype for predicting BMI.[31]
- A significant association was observed between a SNP located within the TAS2R38 gene (the PROP-insensitive allele) and increased eating disinhibition in women.[32] This was not confirmed in a later study.[38]
- Genetic variants within or near bitter taste receptor genes have been investigated for associations with alcohol consumption. Alleles that decrease the sensitivity of the receptor lead to increased intake of alcohol.[43] Of the four studies investigating genetic variants of TAS2R38, the results for three were statistically significant. In one study, the association was found in women of African-American families but not in European Americans of either sex.[38,44-46] Although PROP bitterness (taster status) may explain more of the variance in alcohol intake than did the TAS2R38 genotype.[46] An allele of TAS2R16 is associated with alcohol consumption in African American families and risk for alcohol dependence: increased bitter taste sensitivity lowers maximum drinks consumed in a 24-hour period[46] and the risk for alcohol dependence.[47] No evidence was found indicating that genetic variation in TAS2R38 is a risk factor for alcohol dependence.[46]
- A polymorphism of the TAS2R16 gene has shown a statistically significant association with longevity. The variant allele was associated with a decreased probability to attain longevity.[48]
- Individuals with one or two nonfunctional TAS2R38 alleles are more likely have a sinonasal gram-negative bacterial infection than those with two functional receptor alleles,[49] although the potential for therapeutic benefit from agonists in preventing upper respiratory infections appears to require topical application.[49,50]

Quinine and denatonium benzoate are bitter substances known to stimulate many bitter taste receptors. Clinical studies have investigated their effect on aspects of digestion.

- Two randomised, double-blind, placebo-controlled, crossover studies with healthy volunteers administered quinine by intraduodenal infusion or enteric-coated capsule, in order to bypass stimulation of receptors in the mouth. No effect on food intake was found for one study, the other found a decrease, particularly in PTC tasters. The results were similar for blood levels of cholecystokinin (increase in one study; no effect in the other). In the one study that measured these parameters, no changes were observed in plasma concentrations of GLP-1 or PYY (peptide YY). The difference in dosage does not explain the variation in the results.[51,52] Quinine administered intragastrically did not slow gastric emptying,[53] although gastric emptying was slowed when quinine was tasted but not swallowed.[54]
- A series of tests with healthy volunteers found that an intragastric dose of denatonium benzoate reduced hunger and increased satiation.[55-60] Although TAS2Rs were found in human gastric smooth muscle cells and bitter substances were able to induce a response in these cells (using the calcium imaging assay), and a TASR2-dependent delay in gastric emptying was observed in mice,[60] there was no effect on gastric emptying in healthy volunteers.[59]

A concentrated hop extract that is used to increase the bitterness of beer after fermentation has been evaluated in a randomised, double-blind trial for potential effects in prediabetes. Participants received one of three doses of hop extract in capsules, containing the bitter isohumulones (isohumulone, isocohumulone, isoadhumulone; 16, 32 or 48 mg/day), or placebo for 12 weeks. Significant decreases in body mass index and total fat area compared to placebo at 12 weeks were found for those taking the highest dose (48 mg/day) of isohumulones. This group also recorded a significant reduction in HbA1c compared to placebo at 12 weeks. Fasting blood glucose significantly decreased from week 4 compared to baseline values for the 32- and 48-mg/day dose groups, but did not change in the placebo group (statistical significance not determined).[61] (The major alpha-acids (humulone, cohumulone, adhumulone), present in dried hops (*Humulus lupulus* strobiles), undergo isomerisation, producing the iso-alpha-acids, under the action of heat, for

example, when boiled during beer brewing. In comparison to the alpha-acids, the iso-alpha-acids are intensely bitter.[62,63] Iso-alpha-acids are unlikely to be present in galenical herbal products unless high temperatures were used in the manufacture.)

Summary

Bitter taste receptors have been found in many tissues of the body including the lower gut. Herbal constituents have been found to stimulate a proportion of these receptors *in vitro*. The new bitter taste receptor research combined with physiological knowledge of the gastrointestinal tract suggest potential new uses for bitter herbs. This includes particularly, a role in glucose metabolism as suggested by the berberine research. In those individuals with a reduced functioning in taste receptors, bitter herbs may help reduce alcohol consumption and potentially improve longevity. Ongoing research may strengthen the evidence for a role in satiation and obesity.

The Classic View of Bitters

Bitter-tasting herbs have a long tradition of use. The pre-dinner drink (aperitif) had its origin in the Roman practice of drinking wine infused with bitter herbs to help ensure efficient digestion.[64] In western herbal medicine bitters are used to stimulate the appetite and digestive enzymes and to treat associated conditions such as dyspepsia, indigestion, sluggish gallbladder function and food intolerance.[65] Bitters were also regarded as having tonic and wider applications, such as to treat fatigue and debilitated conditions affecting the whole body.[65-67]

Pharmacological investigations and hypothesising undertaken since the early 20th century has suggested possible mechanisms for the traditional digestive action of bitters:[68,69]

- A local response in the mouth, in which the taste buds are stimulated, leading to secretion of saliva and gastric juices possibly mediated by a reflex involving stimulation of the vagus nerve. The effect is likely to be most marked in conditions where digestion is below optimum, where a positive effect on appetite is also observed. (The presence of taste receptors in the mouth support this.)
- A cephalic response i.e. responses originating from the brain, in which the action on the gustatory nerves in the mouth reflexively leads to a dilation of the gastric vessels and increase in gastric and salivary secretions.
  - The bitter stimuli could pass via the glossopharyngeal nerve to cells in the cerebral cortex, and then to the salivary gland and stomach via the vagus nerve.
  - This would also give rise to an increase in the secretion of bile.
  - It is possible that local stimulation accentuates the cephalic-elicited vagal stimulation.
- A direct effect on the stomach. A rise in salivation and gastric acid production, and relief of symptoms due to indigestion has been demonstrated in uncontrolled conditions, when bitters were administered directly into the stomach. *For example, see Gentian section below*. (The presence of taste receptors in the stomach supports this.)
- Sympathetic nervous system stimulation, in which the appetite-inducing action is due to improved circulation in the abdominal organs.

Stimulation via the vagus nerve results not only in an increase in gastric acid and pepsin secretion, but a transient rise in gastrin, a slight increase in gallbladder motility and a priming of the pancreas. Therefore, bitters could have a promoting effect on all components of upper digestive function, namely the stomach, liver and pancreas. It was thought that bitters needed to be tasted, and for a direct effect on the gastric mucosa, higher doses than the usual traditional ones would be needed.[68]

Bitter Tonics & Other Digestive Herbs

Gentian

Gentiana lutea root contains secoiridoid bitter glycosides including gentiopicroside (also known as gentiopicrin) and the extremely bitter amarogentin, among other constituents.[70,71] The European Pharmacopoeia specifies that Gentian root (1:1000 decoction) should have a bitterness value of not less than 10 000. The bitterness value is determined by comparison with quinine hydrochloride which has a bitterness value set at 200 000.[72]

Gentian, as a bitter tonic, is traditionally used for loss of appetite, dyspepsia; to provide tone to the gastrointestinal tract and to assist recovery after prolonged fever or infection such as improving assimilation of food. It is specifically indicated, by the Eclectic physicians, for reduced digestion with physical and mental weariness.[73,74]

In healthy volunteers, a small, single dose of Gentian tincture induced a significant increase in salivary secretion.[75] One oral dose of an alcoholic extract of Gentian (containing 0.2 g root) given to volunteers 5 minutes before a meal stimulated gastric secretion, release of bile from the gallbladder and bile production by the liver.[76]

In a multicentre, uncontrolled study, 205 patients with various dyspeptic symptoms took on average about five capsules per day, each containing 120 mg of a 5:1 dry extract of gentian root (corresponding to a total of 2.9 g/day, dried root), for 15 days. Rapid relief of symptoms such as constipation, flatulence, appetite loss, vomiting, heartburn, abdominal pain and nausea was achieved.[77] These observed therapeutic effects for Gentian taken as capsules that were not tasted, could be readily

explained by the presence of bitter receptors in the lower gastrointestinal tract.

Ginger

Ginger has been cultivated and used medicinally in India and China since antiquity. The Italian physician, Dioscorides in the first century AD praised ginger: "it is of a heating and digestive quality, and is profitable for the stomach".[78,79]

Ginger is used throughout the world as a medicinal agent. With regard to the digestive system it is primarily a carminative and digestive stimulant in the traditional systems of the west, China, India, Indonesia, Thailand, South Africa and South America, where it is used to treat stomach ache (especially when due to undigested food), poor appetite, dyspepsia, flatulence and nausea. In western traditional medicine Ginger is also considered to be a circulatory stimulant and has been used for stomach cramps due to cold. The Eclectics recommended it to stimulate and restore tone to the gastrointestinal tract. In traditional Chinese medicine (TCM) dried Ginger rhizome is listed in the Chinese Pharmacopoeia with an indication of epigastric pain with cold feeling. Ginger is also antispasmodic and is beneficial for colic.[74,80-87] The German Commission E recommends Ginger for the treatment of dyspepsia.[88]

Pungent spices (including Ginger) are common additions to Ayurvedic formulas, and may play a role in increasing the bioavailability of other substances.[89]

A Thai controlled study with healthy volunteers found that a single dose of Ginger (1 g dry powder suspended in water) produced an increase in relaxation of lower oesophageal sphincter (LOS) during swallowing without affecting basal LOS pressure. Ginger may therefore assist patients with gaseous abdominal distension.[90] In healthy volunteers Ginger improved gastroduodenal motility, but a conclusive effect has not been demonstrated on gastric emptying rate.[91-93] Although Ginger (single dose, 1.2 g dried powder) stimulated gastric emptying in a small number of patients with functional dyspepsia, there was no impact on gastrointestinal symptoms or gut peptides (motilin, ghrelin, GLP-1).[94]

Two randomised, controlled trials have investigated the effect of ongoing treatment with Ginger in obese volunteers in Iran.[95,96] Ginger was prescribed as tablets or capsules and participants maintained their diet and physical activity levels throughout the trials. Slight but statistically significant reductions compared to placebo were observed for some parameters e.g. body weight (-0.95 kg), body mass index (BMI) and waist circumference (-1.25 cm) in women treated for 12 weeks with 2 g/day dried powder. Total appetite score was also significantly decreased. The results were stronger in those with a particular genotype.[95] No effect was observed on BMI, or waist circumference in men treated with 1 g/day dried powder for 10 weeks.[96]

Chen Pi (Tangerine)

Citrus reticulata dried peel of the ripe fruit is regarded in TCM as a carminative, stomachic and expectorant. It is used to increase gastric secretion and peristalsis, to stimulate appetite and relieve abdominal distension, and may be used to treat flatulence and nausea.[97-100] The literal English translation of Chen Pi is "aged peel". Chen Pi has a bitter and acrid taste with a "warm" property.[99] The Chinese Pharmacopoeia recommends Chen Pi for sensation of fullness in the chest and epigastrum (possibly indigestion) with anorexia, vomiting and diarrhoea.[82] The cold pressed essential oil of Chen Pi will support the activity of Chen Pi ripe fruit peel.

Wormwood

Artemisia absinthium leaf or leaf and flowering tops is the other classic, well-known bitter herb. It is used traditionally to treat appetite loss, disturbed digestion, flatulence,[73] disordered bile flow[88] and debility.[101] Wormwood has also been recommended for postinfectious conditions, to enhance resistance (having a general strengthening effect) and relieve any subsequent fatigue, low vitality and reduced digestion.[66]

Wormwood given to human volunteers 5 minutes before a meal stimulated gastric secretion.[76] Another study found that single dose of Wormwood to patients with liver diseases caused a dramatic increase in duodenal levels of pancreatic enzymes and bile.[102]

Feverfew

Feverfew leaf was regarded by Eclectic physicians as:

- a tonic that influences the whole intestinal tract, specifically increasing appetite and improving digestion; useful for colic, flatulence, belching and general indigestion;[73,103]
- having a mild circulatory stimulant effect.[103]

Herbalists in the United Kingdom also regarded Feverfew as a bitter and a general tonic.[101]

Safety

- Mild adverse effects (flatulence, stomach cramp, nausea, headache) were observed in 2.4% patients taking an average dose of Gentian extract corresponding to 2.9 g/day of dried root.[77] Occasional headache and nausea has been reported.[70,104] The chance of experiencing nausea increases for high doses taken in liquid form.[68]
- Contraindicated in known allergy to Wormwood,

Feverfew, parthenolide or plants of the daisy family.

- Caution is advised for patients with hyperacidity, gastric inflammation or gastric ulceration when taking bitters (this originates from the Classic understanding) and Ginger.
- Wormwood is contraindicated in pregnancy and lactation. Substantial doses of Feverfew (e.g. more than 0.3 g/day, dried herb) should not be taken when pregnant. A daily dose of 2 g of dried Ginger should not be exceeded in pregnancy.
- Daily doses of dried Ginger in excess of 4 g should be prescribed with caution in patients who are already taking blood-thinning drugs such as warfarin or aspirin or who have increased risk of haemorrhage.
- It has been recommended that Wormwood, taken as an infusion, not be taken continuously for more than 4 weeks at a time. It can be prescribed again for short periods if needed.[66] The possible thujone content of Wormwood also limits high dosages to the short term.

Supportive Formulation

These herbs complement each other to provide a bitter tonic effect, which supports digestive function and general health.

Indications

- Poor appetite, sluggish digestion, dyspepsia, flatulence.
- As a digestive and tonic during convalescence.
- Food intolerances and allergies.
- As part of a regimen to improve nutrient absorption and regain healthy bowel flora.
- Possibly as a part of a regimen to support glucose homeostasis, although higher than usual doses may be required, and weight loss.

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