

## Functional foods with digestion-enhancing properties

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### Abstract

On analyzing the traditional societies' plant lore by treatment and plant categories, one cannot but notice the greater weight given to treatment of digestive disturbances and ailments compared to modern Western pharmacopoeias, and the blurred boundaries between medicines and foods, in contrast to the clear-cut distinction made in contemporary industrialized societies. Hence, there is an interest in exploring the issue of multifunctional food and traditional ingredients with digestive properties. In this paper, I examine the coevolutionary foundations for digestive activities, the problems and ambiguities that emerge in the analysis of traditional data, and the possible biological mechanisms underlying the actions of bitter, aromatic and pungent compounds. After these premises, this paper presents a short review of those plants with a significant body of research supporting the claims that they have a digestive action, with particular emphasis on clinical data. The plants that have a substantial body of data in support of their digestion-enhancing activities mainly belong to one of three groups: bitter, aromatic and pungent plants. Amongst the most important we can find ginger, peppermint, aniseed and fennel, citrus fruits, dandelion and artichoke, melissa and chamomile, but many more have a significant body of experimental data available.

**Keywords:** medicinal foods, spices, TAS2R, TRP, ethnobotany

### Introduction: plants used for gastrointestinal complaints in the folk traditions

Modern ethnobotanical literature shows that indigenous plant remedies and functional foods (FFs) are focused, more than Western pharmacopoeias, on gastrointestinal (GI) disorders, which represent 10%–50% of the indications (see e.g. Etkin and Ross 1994; Balick and Cox 1996; Pieroni and Price 2006).

One possible explanation for this trend is that the genus *Homo* had to evolve in a world rich in alimentary toxins, and had to develop a system of detection, management and defence against those same toxins. The GI tract, the first diaphragm between the external world (xenobiotics) and the internal physiology, is the site for this system and hence a preferred site of interaction with medicinal plants and FF (Johns 1990).

### FF used for GI complaints in the folk traditions

Two main *data* that emerge from a review of FF used worldwide for digestive complaints, supported by other published data:

- A significant percentage, between 20% and 56% (on average 40%), of edible wild plants is used in traditional societies as a medicine (Pieroni and Price 2006).
- There is a high prevalence of species belonging to three taxa – Asteraceae, Lamiaceae and Apiaceae – and of species containing molecules belonging to three phytochemical groups: essential oils, bitter compounds and pungent compounds (Leonti et al. 2006; Ali-Shtayeh et al. 2008).

### Coevolution and gut sensorium

A recent model of neurohumoral control of GI function seems to be able to connect these apparently disconnected data. According to this model, the GI tract can be seen as a sense organ (via tastant-sensing cells) that has coevolved with some phytochemicals (such as bitter or pungent compounds), and which allows their detection and appropriate response by means of paracrine and endocrine release (Kitamura et al. 2010). Bitter and pungent taste receptors are the main mediators of these actions (see Figure 1).

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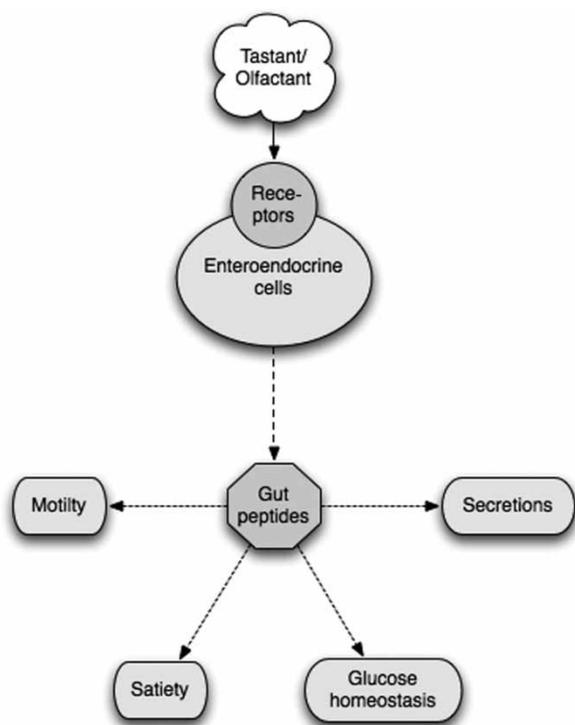


Figure 1. Tastant receptors in the gastrointestinal tract as mediators of local and systemic responses via paracrine and endocrine release of peptides.

### Bitter receptors

In *Homo* and in mammals, the capacity to detect the presence of toxic substances is strongly associated with the development of bitter receptors (taste receptor type 2 – TAS2R) in the oral cavity, an evolutionary-conserved mechanism to prevent ingestion of bitter-tasting dietary toxins (Meyerhof et al. 2005; Scott 2005) (see Table I).

In the last 10 years, there have been various reports on the presence of the receptors in extraoral sites, with non-gustatory functions (Wu et al. 2002), whose activation promotes the release of GI peptides, in particular cholecystokinin (CCK) (Dockray 2003; Flemstrom and Sjoblom 2005). This in turn triggers the release of pancreatic enzymes and of bile salts, regulates GI motility, gastric acid secretion, inhibits gastric emptying (Wicks et al. 2005) and satiation (Sternini 2007). Bitter receptor activation, mediated by CCK, seems to be aimed at reducing the absorption of the bitter compounds and at maximizing the

Table I. Members of the TAS2R family and bitter phytochemicals shown to bind to them.

TAS2R receptors	Active molecules
TAS2R10	Strychnine, humulones
TAS2R14	Picrotoxin, $\alpha$ -thujone
TAS2R16	Salicin
TAS2R43/44	Aristolochic acid
TAS2R50	Andrographolide, amarogentin

absorption of complex carbohydrates, essential fatty acids and fat-soluble vitamins (Jeon et al. 2008) (see Figure 2).

### Pungent receptors

A set of ion channels [transient receptor potential (TRP) channels] expressed in the gut responds to a varied class of pungent compounds (see Figure 3 and Table II)

### A repertoire of digestive plants

The plants analyzed in the following section represent but a very small percentage of the FFs with a tradition of digestive use. The plants were chosen on the basis of existent clinical and experimental data on digestion-enhancing effects, irrespective of representativeness in the diet.

The Bitter Artichoke (*Cynara cardunculus* subsp. *cardunculus* Hayek – Asteraceae) (cfr. Valussi 2011 and references therein) was traditionally used as a digestive and liver aid, to help stimulate the appetite, provide relief from nausea, stomach ache, flatulence and a sense of fullness, and both the German Commission E and the ESCOP monograph approve of its use for digestive problems. It contains bitter sesquiterpene lactones (e.g. cynaropicrin) that might bind to receptor TAS2R46 (Brockhoff et al. 2007).

A mode of action randomized, double-blind clinical study on 20 subjects with acute or chronic metabolic disorders showed that intraduodenal administration caused a 100%–150% peak increase in bile 1 h later, which lasted for 3 h.

A post-marketing surveillance study on 417 patients with hepatic and biliary tract disease showed elimination of abdominal pain, bloating, flatulence, constipation, lack of appetite and nausea in about 80% of patients after 4 weeks.

A second post-marketing study including 553 subjects with dyspepsia showed a clinically relevant reduction of dyspeptic symptoms in 71% of the subjects within 6 weeks of treatment. A patient subset with key symptoms of irritable bowel syndrome (IBS) experienced significant reductions in symptoms (emesis, nausea, abdominal pain).

In a similar open study on 203 subjects with dyspepsia, there was an average reduction of 66% of the symptoms. The global efficacy was evaluated by the physicians as being good or excellent in 85.7% of the cases. In a more recent double-blind, randomized controlled trial vs. placebo on 244 patients with functional dyspepsia the *verum* treatment reduced symptoms and improved the quality of life after 6 weeks.

In an open study on 454 patients with dyspepsia, the dry extract reduced 40% of the global dyspepsia score. A subset analysis of the study on subjects suffering

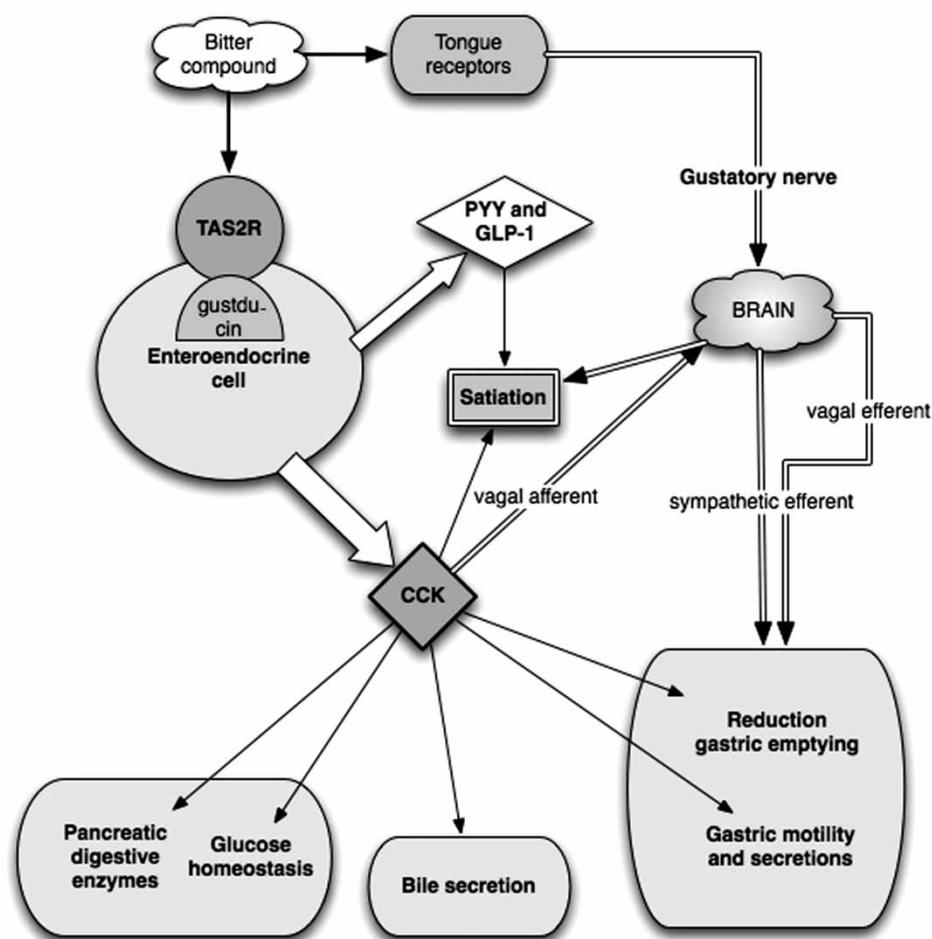


Figure 2. The relationships between bitter receptors activation, gut peptide release, CNS activation and gastrointestinal effects.

from IBS showed a significant fall in disease incidence of 26.4%.

When consumed by 30 subjects as ingredient of an iced dessert, the extract intensified the positive effects of the dessert on the symptoms of functional dyspepsia.

A prospective cohort study on 311 patients with functional dyspepsia analyzed the efficacy of a mixture of dry extracts of artichoke leaf, dandelion radix and turmeric rhizome, plus rosemary micro-encapsulated essential oil. After 60 days of treatment, a statistically significant gradual reduction in symptom severity was noted, and a global clinical response was recorded in 38% of patients.

Dandelion (*Taraxacum officinale* G.H. Weber ex F. H. Wigg – Asteraceae) roots and leaves (cfr. Valussi 2011 and references therein) have been used extensively since ancient times in Europe as a bitter tonic and for the treatment of various disorders such as dyspepsia, heartburn, spleen and liver complaints, hepatitis and anorexia. Both Commission E and ESCOP support using *T. officinale* to treat disturbed bile flow, loss of appetite and dyspepsia. It contains bitter sesquiterpene lactones (e.g. eudesmanolides,

guaianolides) which might bind to receptor TAS2R46 (Brockhoff et al. 2007).

An herbal combination containing *Calendula officinalis*, *T. officinale*, *Hypericum perforatum*, *Melissa officinale* and *Foeniculum vulgare* reduced intestinal pain in 96% of 24 patients by the 15th day in an uncontrolled trial involving patients with chronic colitis. Defecation was normalized in patients with diarrhoea syndrome.

A prospective cohort study on 311 patients with functional dyspepsia analyzed the efficacy of a mixture of dry extracts of artichoke leaf, dandelion radix, turmeric rhizome and rosemary essential oil. After 60 days of treatment, a statistically significant gradual reduction in symptom severity was noted, and a global clinical response – defined as a 50% reduction in the total scores of all symptoms – was recorded in 38% of patients in 30 days.

The Lemon fruit (*Citrus limon* (L.) Burmann fil. – Rutaceae) (cfr. Valussi 2011 and references therein) has been used both in the West and in the East as a tonic digestive, strongly aromatic and slightly bitter, used in decoction and alcoholic extracts. The juice has traditionally been used as a digestive, astringent, stomachic, antispasmodic and carminative, used

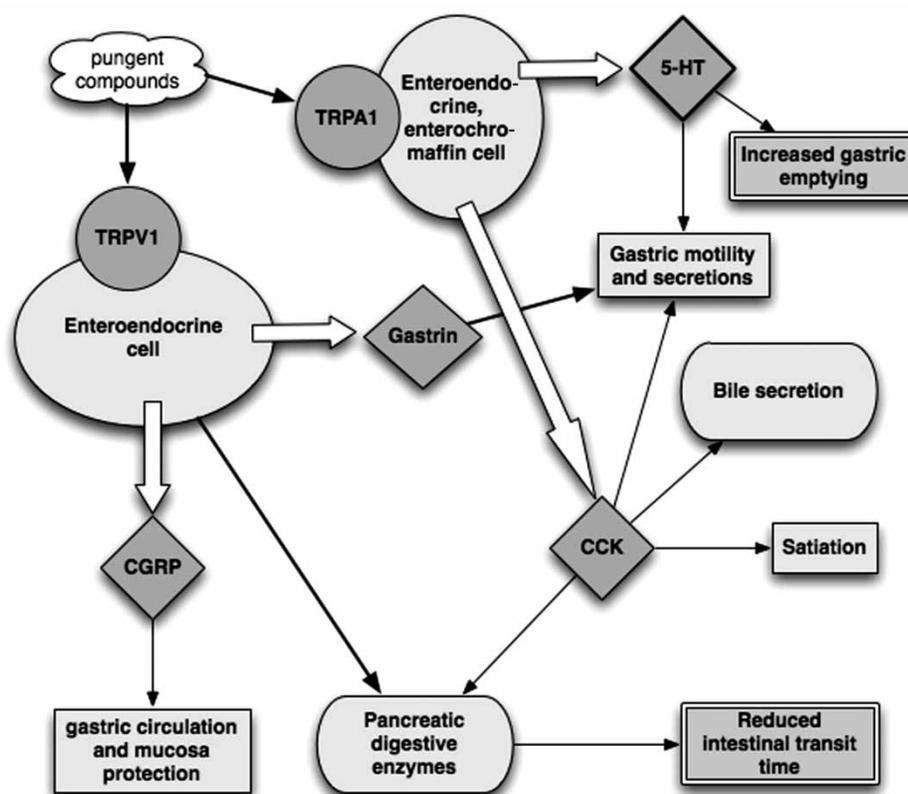


Figure 3. The relationships between pungent receptors activation, gut peptide release, and gastrointestinal effects.

for the treatment of inappetence, gastralgia, nausea and gastric acid reflux. The rind contains a bitter compound, the nortriterpene limonin, which activates the receptor TAS2R38 (Meyerhof et al. 2010).

It is well known that both lemon aroma and flavour influence the cephalic phase of digestion (salivation). In an interesting study comparing the effects of different visual stimuli, Christensen and Navazech show that there is a stronger response (a higher salivary

volume) to visual stimuli of acidic (lemon juice) and pungent foods (pizza with hot peppers). Both lemon odour and the introduction of lemon juice in the oral cavity cause an increase in the volume of saliva, statistically higher than that caused by a non-stimulus (pure air or pure water).

The study by Bauslaugh showed a relationship between salivation and GI motility during olfactory stimulation (Bauslaugh 1994), and it is well

Table II. Effects of phytochemicals shown to bind to different TRP channels.

TRP channels	Active molecules	Effects
Vanilloid channel TRPV1	Capsaicin, piperine, allicin, gingerols, shogaols, zingerone, camphor, en-docannabinoids	Piperine increases pancreatic activity, reduces intestinal transit time (Purhonen et al. 2008). Capsaicin targets duodenal receptors, stimulates gastrin secretion (Kidd et al. 2009), evokes dyspeptic symptoms acutely, reduces them if used chronically, affects gastric sensorimotor function (van Boxel et al. 2010), stimulates (at low doses) CGRP secretions, which in turn stimulates microcirculation and protects gastric mucosa from irritant compounds (Abdel-Salam et al. 1997). Shogaol induced nociceptive responses via TRPV1 in rats. Zingerone desensitized rat neurons by repeated applications (Iwasaki et al. 2006)
Melastatin channel TRPM8	Menthol 1,8-cineole	Menthol causes cold hyperalgesia (Namer et al. 2005)
TRPA1 channel	Allyl isothiocyanate, methyl salicylate, eugenol, cinnamaldehyde	Stimulation causes serotonin release, 5-HT <sub>3</sub> receptor-mediated contraction of isolated strips of intestine, stimulation of vagal afferents and enteric nerves, and of various GI reactions (vomiting, peristaltic reflux) (Nozawa et al. 2009). At duodenal level seems to mediate the release of CCK. (Purhonen et al. 2008)

known that pepsinogen, gastrin and HCl secretions are influenced by cephalic stimulations, hence possibly by the organoleptic stimulation by lemon juice.

Apart from sensory activities, lemon juice can directly affect GI secretions. Hundred microliters of orange and lemon juice have shown very potent stimulant action on pancreatic secretion compared to other stimuli, and the peak response was observed earlier.

In general, the juice stimulated a response quantitatively and qualitatively comparable to that of secretin.

The fruits of Fennel (*F. vulgare* Mill. – Apiaceae) (cfr. Valussi 2011 and references therein) are commonly employed as a culinary herb and as a remedy to improve digestion in traditional systems of medicine; they have been used since ancient Roman and Egyptian times as a valuable warming carminative and aromatic digestive, used for dyspepsia, bloating, flatulence and poor appetite.

A randomized, placebo-controlled trial tested a fennel seed oil emulsion on 125 infants with colics. It eliminated colic in 65% of infants, compared to 23.7% in the control group.

A mixture containing chamomile (*Matricaria recutita*), fennel (*F. vulgare*) and lemon balm (*M. officinalis*) was found to have significant benefits in the treatment of infantile colics in a double-blind, placebo-controlled study on 93 breast-fed infants treated twice a day for 1 week, although according to two subsequent experimental studies in rats the major contribution to the antispasmodic activity was due to *M. recutita* and *M. officinalis*.

In an uncontrolled clinical study on 24 patients with chronic non-specific colitis, a herbal combination of *T. officinale*, *Hipericum perforatum*, *M. officinalis*, *C. officinalis* and *F. vulgare* eliminated spontaneous and palpable pains along the large intestine in 95.83% of the patients.

The essential oil seems able to reduce smooth muscle spasms in various *in vitro* models, but this activity seems concentration dependent, with spasmogenic effect at lower doses, and spasmolytic at higher ones.

The ethanol extract and the aqueous infusion show spasmolytic effects.

In animal models, the administration of fennel increased spontaneous gastric motility and gastric acid secretions.

The admixture of 0.5% fennel fruits to the diet of rats for 6 weeks reduced the food transit time by 12%, while the admixture of fennel fruits (0.5%) and mint (1%) for 8 weeks stimulated a higher rate of secretion of bile acids in rats and a significant enhancement of secreted intestinal enzymes, particularly lipase and amylase.

Lemon balm (*M. officinalis* L. – Lamiaceae) (cfr. Valussi 2011 and references therein) is a very popular

traditional herb used in infusion for restlessness and dyspepsia, especially among children.

A randomized, double-blind, placebo-controlled trial testing lemon balm in combination with chamomile and fennel showed significant improvement of infantile colics.

A fixed commercial combination of extracts of *M. officinalis*, *Mentha spicata*, and *Coriandrum sativum* was tested on 32 IBS patients and compared with placebo for 8 weeks in a clinical study. The study shows that the combination reduces the severity and frequency of abdominal pain and of bloating better than placebo.

The ethanol extracts and the essential oil have shown inhibition of artificially induced contraction of smooth muscles, but there are also contrasting data.

Peppermint (*Mentha x piperita* L. – Lamiaceae) (cfr. Valussi 2011 and references therein) has always been used in traditional learned and folk medicine as a carminative, antispasmodic, antiemetic and digestive, both in the West and in the East. The plant contains an essential oil characterized by the presence of the alcohol menthol, which binds to the melastatin channel TRPM8, causing cold hyperalgesia (Namer et al. 2005).

The essential oil reduces intracolonic pressure. In an open study of 20 patients, peppermint essential oil used alongside a colonoscope relieved colonic spasms, and it had the same effect when administered with barium enemas.

The essential oil is also able to reduce tension in hypertonic intestinal smooth muscle in case of IBS.

In healthy volunteers, intragastric administration of a dose equivalent to 180 mg peppermint oil, reduced intraoesophageal pressure within 1–7 min of infusion.

Oral administration of the essential oil delayed the gastric emptying time in healthy volunteers and in patients with dyspepsia, and it slowed small intestinal transit time in 12 healthy volunteers.

A combination of essential oils (peppermint and caraway) produced smooth muscle relaxation of stomach and duodenum; in a double-blind, placebo-controlled multicentric trial with 45 patients, it improved symptoms of dyspepsia, reducing pain in 89.5% of patients and improving clinical global impression scores in 94.5% of patients.

The same combination tested on 223 dyspeptic patients in a prospective, randomized and double-blind controlled multicentric trial, significantly reduced pain, and when tested on 96 outpatients with dyspepsia significantly reduced pain by 40% and reduced sensations of pressure, heaviness and fullness.

The formula was shown to be as effective as cisapride in reducing both the magnitude and frequency of pain, and it had a relaxing effect on the gallbladder.

In a systematic review of herbal medicines for functional dyspepsia, the authors found 17 randomized clinical trials, nine of which involved peppermint

and caraway combination preparations. Symptoms were reduced by all treatments; 60%–95% of patients reported improvements in symptoms.

Choleretic activity has been demonstrated in animal models for the herb, various flavonoid fractions, flavomentin, the essential oil, and menthol. The effect probably derives from the spasmolytic activity of menthol and other terpenes on the Oddi's sphincter.

The antiemetic and prokinetic effects of peppermint oil and of (-)-menthol are due at least partly to the binding to the 5-HT(3) receptor ion-channel complex, in a manner similar to that of ginger.

Chamomile (*Matricaria chamomilla* L. – Asteraceae) (cfr. Valussi 2011 and references therein) has been a highly popular family herb since antiquity, generally used for nervous excitability and digestive disorders, stomach cramping, dyspepsia and flatulence.

In an open, multicentric study, 104 patients with GI complaints (gastritis, flatulence and mild intestinal spasms) were treated for 6 weeks with an oral chamomile extract (standardized for 0.05% alpha-bisabolol and 0.15% apigenin-7-glucoside), with 44.2% of subjects self-reporting to be symptom free.

In a double-blind study, a herbal decoction (150 ml/day containing *M. chamomilla*, *Verbena officinalis*, *Glycyrrhiza glabra*, *F. vulgare* and *M. officinalis*) was tested for 7 days on 68 healthy infants with colic. Fifty-seven percentage of the infants experienced relief compared to 26% in the placebo group.

Whole extracts and isolated components demonstrate a dose-dependent antispasmodic effect *in vitro*. The major activity was related to (-)- $\alpha$ -bisabolol, the cis-spiroethers and the flavonoids (in particular, apigenin).

Ginger rhizome (*Zingiber officinale* Roscoe – Zingiberaceae) (cfr. Valussi 2011 and references therein) is probably one of the oldest domesticated spices in human history. It has a prominent role in Asian systems of medicine where it is used for the treatment of dyspepsia, flatulence, colic, vomiting, diarrhoea, spasms and for stimulating the appetite.

It contains an essential oil (1–4%) and a pungent resin, and it stimulates the flow of saliva, bile and gastric secretions (Platel and Srinivasan 2000). Some of the components of the oleo-resin (shogaols, gingerols, zingerone) bind to the vanilloid channel TRPV1, with capsaicin-like nociceptive responses and desensitization effects. The essential oil activates receptor TRPA1 (Bandell et al. 2004).

An extract containing the oleoresin and administered intraduodenally to rats produced an increase in the bile secretion, and it was shown that [6]-gingerol and [10]-gingerol were mainly responsible for the cholagogic effect. An oral dose of ginger enhanced rat pancreatic lipase, sucrase, and maltase activity and stimulated trypsin and chymotrypsin.

The essential oil, a 95% ethanol extract, a hot water extract and of a formula containing ginger, *Pinellia*

*ternata*, *Citrus aurantium*, *Pachyma hoelen* and *G. glabra* were all shown to possess antispasmodic activity on intestinal smooth muscles.

In a clinical study, ginger consumed before meals, increased the number and frequency of contractions in the *corpus* and in the *antrum*, and frequency of contractions in the duodenum; when consumed after meals it was less active.

Both ginger and a Japanese formula (*Dai-Kenchu-To*) containing ginger, *Zanthoxylum* fruit and ginseng root induced phasic contractions in the gastric *antrum*.

Previous clinical data had shown that ginger did not affect the gastric emptying rate but the studies used low dosages of ginger rhizome.

The prokinetic activity was confirmed in other *in vitro* and *in vivo* tests. Ginger extracts had a spasmogenic effect and enhanced the intestinal transit of charcoal meal. At the same time, they showed spasmolytic activity at the intestinal level, probably through a  $Ca^{2+}$  antagonist effect.

Various constituents found in ginger, 6-, 8- and 10-gingerol, 6-shogaol, and galanolactone, act as serotonin receptor antagonists, which could explain the antispasmodic effects on visceral smooth muscle. They could exert their effect by binding to receptors in the signal cascade behind the 5-HT(3) receptor ion-channel complex, perhaps substance P receptors or muscarinic receptors.

At the same time, two compounds (10-shogaol and 1-dehydro-6-gingerdione), and particularly the whole lipophilic extract have shown to partially activate the 5-HT(1A) receptor (20–60% of maximal activation).

The serotonin receptor antagonist activity may partly explain the antiemetic effect of ginger, since these receptors do mediate peristalsis and emesis, and the constituents active on these receptors were also active as anticholinergic antiemetics, in the following descending order of potency: 6-shogaol > or = 8-gingerol > 10-gingerol > or = 6-gingerol.

Many clinical studies have shown the positive antiemetic effects (prevention and treatment of nausea) of ginger and many of its constituents under different circumstances. A systematic review of six controlled studies found that ginger was more effective than placebo in some studies of post-operative nausea and vomiting.

A recent Cochrane review on 20 trials concluded that ginger might be of benefit in case of nausea and emesis, but that the evidence to date was weak.

Hot pepper (*Capsicum annum* L. – Solanaceae) (cfr. Valussi 2011 and references therein) is a native American plant that has been exported all over the world. Capsicum's main active chemical group is that of the capsaicinoids, a group of pungent alkaloids whose prototype is capsaicin (8-methyl-N-vanillyl-6-nonenamide), which binds to the duodenal vanilloid channel TRPV1, affecting gastric sensorimotor function, stimulating gastrin secretion and (at low doses) calcitonin gene-related peptide (CGRP) secretions,

which in turn stimulates microcirculation and protects gastric mucosa from irritant compounds.

The scientific evidence about capsicum and capsaicinoids and their effects on the GI tract is rather contrasting. Capsaicin interacts with the vanilloid receptor and this interaction causes a selective impairment of the activity of nociceptive C-type fibres, causing, on chronic dosage, analgesic and anti-inflammatory effects. These have been evaluated in patients suffering from heartburn and functional dyspepsia, with encouraging results.

The data on gastric secretions and motility are less clear: some studies found a stimulation of gastric emptying and of secretions, others found no difference and others even found a reduction in activity.

The intake of red pepper has caused a reduced energy intake, suppression of hunger and increased satiety, an activity in line with a possible effect on the secretion of CCK.

Four other plants, namely lemongrass (*Cymbopogon citratus* (DC.) Stapf. – Poaceae), Lemon Verbena (*Aloysia citrodora* Palau – Verbenaceae), Star Anise (*Illicium verum*, Hook. f. – Illiciaceae) and Aniseed (*Pimpinella anisum* L. – Apiaceae) are traditionally used as GI remedies and are interesting essential oil-containing plants with positive experimental data, but do not have a significant corpus of clinical data (cfr. Valussi 2011 and references therein).

## Conclusions

The filter used to select plants examined in depth in this article (clinical and experimental data) has left out a very great number of plants, and has probably favoured those plants which are already well known and categorized as “digestive,” and that for this reason have received a large share of scientific interest. A more comprehensive review is needed, one that would comprise a larger number of plants, comparing and contrasting their phytochemical composition and hypothetical mechanisms of action, and that would take into account the role of accompanying foods in modulating the effects of the plants. Particularly interesting, in the author’s opinion, would be studying the evidence for GI activity of fruits like *Aegle marmelos*, *Emblica officinalis*, *Terminalia* spp., *Ananas comosus*, *Carica papaya*, *Tamarindus indica*, etc., which are closer than bitters and pungent to the paradigmatic FFs, and which are almost always used in a food context.

Within the limits already highlighted, experimental evidence seems to support traditional knowledge about bitter and digestive plants, and in particular gives an evolutionary support to the almost universal use of bitters as GI remedies. The review highlights the fruitfulness of combining ethnobotanical and clinical data with suggestions and conceptual tools from the field of evolutionary theory.

The data also support the hypothesis that the presence of these three groups of plants in the diet could promote better health in a number of ways:

Bitter could be used to reduce the gastric emptying rate (allowing for a longer action of gastric secretions on foodstuff) and enhance the post-gastric digestion of fats and complex carbohydrates. Clinical data also point towards an antidyseptic activity of the examined bitter-tasting plants.

Indirect evidence on functional variants in TAS2R suggests that people with lower sensitivity for bitters exhibit poorer health measure and are more likely linked to alcohol dependency (Wang et al. 2007), adiposity (Tepper et al. 2008), eating disorders (Dotson et al. 2010), altered glucose homeostasis (Straub et al. 2003; Dotson et al. 2008) and body-mass index (Feeney et al. 2011).

The increase in sensation of satiety and the reduction of food intake derived from bitter consumption could explain the link with eating disorders and could help control food intake.

Altogether it seems that bitter plants might influence overeating and compulsive behaviour.

Bile salt metabolites variably stimulate growth in bacterial populations (Parsonett 1995); hence, bitter plants might have an indirect effect on intestinal bacterial population.

Pungent and aromatic plants have shown in some instances to have opposite effects to the bitter ones, for instance in increasing the gastric emptying rate occasionally with antiemetic effects.

Pungent plants seem to be able to generically increase the health and functionality of the GI tract by stimulating gastric secretions, increasing blood flow to the gastric mucosa and reducing GI spasms.

Finally, the study of tastants on GIT receptors could pave the way for therapeutic or preventative interventions with systemic effects that do not need systemic absorption.

**Declaration of interest:** The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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