Zingiberis officinale (Ginger) radix – ***Gentiana lutea*** – *Trigonella foenum graecum* – *Mentha piperita* –leaf – *Foeniculi vulgaris*

Gentian extract

Gentiana lutea

Gentianae radix is known under the common names : German: Großer Enzian, (Berg)-Fieberwurzel, Hochwurzel; Engl.: Bitter wort, Common gentian, Great yellow gentian, Yellow gentian, gentian root; French: Gentiane jaune, Grande gentiane; Ital.: Genziana maggiore.

Constituents: (Wichtl, 2002)
Bitter constituents: Bitter constituents (2-8%) are located mostly in the cortex of the root. Most of the bitter constituents belong to the class of secoiridoid glycosides with gentiopicroside (also known as gentiamarine and gentiopicrine) as main components and a lower amount of amarogentine (0.025 – 0.4%). The occurrence of swertiamarine and sweroside has been reported occasionally. The bitter value of gentiopicroside is 12000; that of amarogentine is 58 mill., the most bitter substance known. The quantity of the bitter constituents depends on the season as well as the age of the roots and the altitude. The total content increases with the altitude and reaches its maximum in spring. Volatile oil:0.1 – 0.2% volatile oil; important mainly in the liqueur-production for giving its characteristic flavour.

Widely used as: Bitter stomachic and stimulant , for Dyspeptic complaints, loss of appetite, flatulence Anorexia e.g. after illness, dyspeptic complaints Gastric complaints, stimulation of appetite, digestive complaints such as loss of appetite, fullness, flatulence

Effects on gastric secretion

in-vitro:

Isolated and enriched parietal cells from rat gastric mucosa were cultured in the presence of EGF (epidermal growth factor) and insulin, expanding the cell population by

170% within 48 h. Determination of the cellular accumulation of radiolabelled aminopyrine was used for indirectly measuring acid production by parietal cells. Addition of 10^{-4} M histamine rose the aminopyrine ratio more than 2-fold within 20 min. When an aqueous dry extract of *Gentiana lutea* L. root was added a concentration dependent rise of the aminopyrine ratio was observed leading to a 1.7-fold stimulation at 100 μg/ml, while cytotoxic effects occurred above 5 mM only. No stimulatory effect was exerted by an artichoke extract. The authors postulated that an aqueous dry Gentiana extract is able to directly stimulate acid production by the gastric mucosa (Gebhardt, 1997). *in-vivo:*
After direct application on the tongue, bitters increase the secretion of gastric fluid during in vivo experiments in dogs (Borissow, 1903). The experiments of Moorhead (1915) in dogs should demonstrate whether the so-called stomachic or bitter tonics, acting in the mouth or in stomach, could affect first the appetite and second the quantity and quality of gastric secretion and cachexia.

In rats, gentian extract increased gastric secretion in a dose-dependent way after direct ingestion in the stomach. Only at the highest concentration of 4% the extract showed an influence on pH: increasing it from 4.25 to 4.85 (Leslie, 1978). Secretolytic effects

in-vivo:

Gentian root infusion (no further information available), administered orally to sheep at a daily dose of 5 g, before feeding produced a stimulant effect on secretion of enzymes in the small intestine (Kazakov, 2003).

As compared to control animals *in vivo* experiments in rabbits demonstrated elevated broncho-secretion after administration of gentian root extract (0.2 g Gentianae radix/ 100g ethanol 19% (V/V)) directly in the stomach by gavage, for 3 days (the equivalent of 12.6 mg/kg/day of dried root). Concerning secretolytic effects significantly increased activity was shown with production rate levels of 37.7% and 104%, respectively, above the control group.

***Trigonella foenum grecum* semen**

Fenugreek seed is rich in mucilage polysaccharides (consisting mainly in galactomannans 25–45%) and contains a small amount of essential oil (0.015%) and a variety of secondary metabolites, including protoalkaloids, trigonelline (up to 0.37%), choline (0.05%); saponins (0.6–1.7%) derived from diosgenin, yamogenin, tigogenin and other compounds; sterols including β-sitosterol; and flavonoids, among which are orientin, isoorientin and isovitexin (WHO, 2007). Furthermore, the nutrition composition of fenugreek seeds is : moisture 2.4 %, protein 30 %, lipids 7 %, saponins 4.8 %, total dietetary fibre 48% (insoluble 28.%, soluble 20%), and ash 3.9 % (WHO, 2003; ESCOP 2003; MURALIDHARA et al, 1999; BRUNETON 1998; RAO et al, 1996; PARIS AND MOYSE, 1967).

Widely used as as appetite stimulant

1. in lack of appetite,
2. orally against gastrointestinal disorders

Only one study dealing with the effect of fenugreek seeds on appetite was located in the literature. Petit et al (1993) showed in rats that oral administration of a hydro-ethanolic seed extract increased food intake and motivation to eat.

Having assayed in rats, dogs in vivo have showed stimulating effect on intestinal motility

While also possess hypoglycaemic activities

PeperMint leaf

The herbal substance consists of whole or cut dried leaf of *Mentha x piperita* L. .
Peppermint is a perennial plant native to Europe, highly aromatic,that may grow as tall as 90cm.

Chemical constituents

The chemical components of peppermint leaves vary with plant maturity, variety, geographical region and processing conditions.

1. The fatty acid composition of the non-polar lipid fraction of peppermint leaves is dominated by palmitic (16:0), linoleic (18:2) and linolenic (18:3) acids (Mckay, 2006).

2. Various flavonoids are present including luteolin and its 7-glycoside, rutin, hesperidin, eriocitrin and highly oxygenated flavones. Other constituents include phenolic acids and small amounts of triterpenes (ESCOP 2003, Julien et al 1984, Litvinenko et al 1975, Croteau & Loomis 1973).

Eriocitrin, with a concentration range of 6.6-15.0%, is the dominant flavonoid glycoside, accompanied by luteolin 7-*0*-rutinoside, hesperidin and rosmarinic acid, on a study of 40 clones of *Mentha piperita* (Guédon et al, 1994)

Chemical composition of the essential oil.

Its major constituents are menthol (30-55%) and menthone (14-32%). Other monoterpenes present are: limonene (1-3,5%), cineole (3,5-8%), menthofuran (1-8%), isomenthone (1,5-10%), menthyl acetate (2,8-10%), pulegone (maxim 3%), carvone (maximum 1%). The ratio of 1,8-cineole content to limonene content is minimum 2 (Eur. Pharm. 8.0).

herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence Treatment of gastrointestinal disorders like flatulence, mild spasm of the gastrointestinal and bile tract, irritable ***Antispasmodic action***

Peppermint leaves

In vitro

Among other studies, alcoholic extracts of Peppermint leaf have showed antispasmodic effects on the isolated guinea pig ileum. 2.5 and 10.0 ml/litre of a Peppermint leaf extract (1:3.5, ethanol 31% w/w) were tested using acetylcholine and histamine as spasmodic agents. Both doses produced a significant increase of the ED_{50}, for acetylcholine and histamine-induced contractions and a significant decrease of the maximum possible contractility. The effect obtained with 10.0 ml/litre corresponded to that of 0.13 mg atropine (effective dose of atropine in the treatment of abdominal spasms: 0.5 – 1.0 mg) (Forster et al, 1980; 1983).
Flavonoids isolated from Peppermint leaf and dissolved in water so that 1 ml corresponded to approximately 0.5 g of dried leaf, inhibited muscular contraction of the guinea pig ileum induced by barium chloride (Lallement-Guilbert et al, 1970).

Aqueous extracts of *Mentha piperitae* showed a significant, dose dependent relaxation effect on isolated rabbit duodenum being the dried leaf extract more effective than the fresh one (Mahmood et al, 2003).
The mode of action on gastric motility of a combination and its individual components

(hydroethanolic herbal extracts from *Iberis amara totalis*, *Menthae piperitae folium* – 1:2.5-3.5, *Matricariae flos, Liquorice root, Angelica radix, Carvi fructus, Cardus marianus fructus, Melissae folium* and *Chelidonium herba*) were studied. Peppermint leaf extract did not show consistent responses in the proximal stomach, inducing relaxation and contraction (Schemann et al, 2006).
On another study in vitro model, was used the same product and some of its isolated compounds. The study was performed to test their activity on histamine-induced contractions and spontaneous motility, of intestinal samples from guinea pig. *Mentha piperita* leaves, as *Iberis amara*, *Melissa folium* had significant effects on decreasing the contraction amplitude (Heinle et al, 2006).

In vivo

In vivo experiments with cannulated dogs Peppermint tea (0.4 g/kg body weight) increased the secretion of bile. Flavonoids, as well as the essential oil, seemed to contribute to this action (Steinegger et al 1992, Pasechnik 1 1966).
Mixed flavonoids from Peppermint leaf (optimum dose 2 mg/kg,), showed choleretic activity in dogs. Flavomentin, a flavonoid preparation from Peppermint leaf, stimulated bile secretion and the synthesis of bile acids in dogs at doses of 0.5-6 mg/kg (optimum 2 mg/kg) (Pasechnik ,1967).

In vivo experiments with cannulated rats, intravenous injection of 0.5 ml of a Peppermint tea (1:5) per rat or a flavonoid preparation (dosage corresponding to 3.3 g of Peppermint leaf per kg) proved effective in increasing the amount of bile acids (Lallement-Guilbert et al, 1970).

Ina study published by Ando et al, 2003, in Holstein steers fed with peppermint, there were lower concentrations in the rumen of ammonia nitrogen and reduction of the numbers of protozoa.

The potential antiulcerogenic, antisecretory and cytoprotective activity of the combination and its individual components (hydroethanolic herbal extracts from Iberis amara totalis, Menthae piperitae folium (Matricariae flos, Liquorice root, Angelica radix, Carvi fructus, Cardus marianus fructus, Melissae folium and Chelidonium herba) were tested in male Wistar rats. A modified formulation of the combination was also tested, taking out three components. Gastric ulcers were induced acutely by indometacin and cimetidine was used as a reference anti-ulcerogenic. The parameters used were the free acidity, mucin and pepsin concentrations in the gastric juice, and the prostaglandin and leukotriene levels in the gastric mucosa. The stomach was histologically examined. Both preparations and their individual components protect the stomach from the ulcerative damage caused by indometacin, inhibiting the release of aggressive factors like acid and leukotrienes, promoting the production of mucin and prostaglandins. This effect could be attributed, according to the authors, to the presence of flavonoids (Khayyal et al, 2001).

Peppermint oil

In vivo

Peppermint oil as a 1 % emulsion exhibited relaxant effects on tracheal smooth muscle of the guinea pig: the I_{50} was 83-91 mg/L (Reiter & Brandt, 1985)
Peppermint oil emulsified with tween, 1% in aqueous solution, relaxed chemically contracted guinea pig taenia coli (I_{50}: 22.1 g/mL) and inhibited spontaneous activity in the guinea pig colon (I_{50}: 25.9 g/mL) and rabbit jejunum (I_{50}: 15.2 g/mL). Using whole cell clamp configuration in these jejunal muscle cells, the potential –dependent calcium currents were inhibited in a dose-dependent manner by peppermint oil. Peppermint oil reduced the peak current amplitude and increased the rate of current decay, indicating a reduction of calcium influx similar to that caused by dihydropyridine calcium antagonists. Peppermint oil demonstrated to inhibit non-competively 5 – hidroxitriptamine (serotonin) and the substance P induced smooth muscle contraction (Hills et al, 1991).
Peppermint oil appears to enhance production of bile. In experiments where bile flowed out of a cannula from an anaesthetized dog, an infusion of peppermint leaves (0.4 g/kg) enhanced bile production. Menthol also produced an enhancement of bile production: 0.06 g/kg in 1 dog

and 0.1-1.0 g/kg in rats. In others experimental studies in animals, menthol and peppermint oil induced a marked and dose related choleresis (Siegers et al., 1991).

Renoprotective action

A study was carried out to evaluate the renoprotective effect of *Mentha piperita* against gentamicin induced nephrotoxicity. Fresh plant leaves of *M. piperita* were collected from, Pakistan. Extraction was done with ethanol after drying the leaves under shade. The ethanol was than evaporated by rotary evaporator (r210, Germany). A total of 24 male rabbits were divided into four groups of 6 each and each group was treated independently, group C with 0.9% saline only 2 ml/kg (i.m) for 21 days, group G with gentamicin 80 mg/kg (i.m) for 21 days, group GM-pi with gentamicin 80 mg/kg (i.m) + *M. piperita* 200 mg/kg (p.o) for 21 days and the group M-pi with *M. piperita* 200 mg/kg (p.o) for 21 days. Three rabbits in each group were sacrificed on day 21 of study period for examination of the kidneys.
Histological examination of the kidneys of Group G showed proximal tubular necrosis with loss of cellular pattern. Glomerular atrophy and ruptured tubules with hydropic changes were also observed while in case of Group C animals' normal tubules with no evidence of necrosis and normal glomeruli or hydropic changes were observed. Groups GM-pi and M-pi also showed normal histology with no common abnormality or significant toxicity. Significant rise in the serum creatinine, blood urea nitrogen and serum uric acid with fall in creatinine clearance were observed in Group G animals when compared with control, which was reversed to almost control values in the extract treated animals. The authors refer that it showed the protective role of *M. piperita* against toxic effects of gentamicin on kidney.
They concluded that concurrent administration *M. piperita* successfully prevented renal damage associated with gentamicin, explored by various biochemical and histological examinations. Further, the study also shows that concomitant use of *M. piperita* does not decline the efficacy of gentamicin with respect to its antibacterial activities (Naveed et al., 2014)

Hepatoprotective action

A study to evaluate the protective activity of leaves of *Mentha piperita* L (Mentha leaves water extract) in adult Swiss mice against arsenic-induced hepatopathy was performed by Shama et al (2006). Pre and post treatment of Mentha with arsenic alters the biochemical parameters in the liver, declining ACP, ALP, SGOT, SGTP and LPO content. A significant increase in body and liver weight, GSH content and LDH activity in liver was estimated. The authors conclude that the results indicate that Mentha extract may be useful in reducing the side effects of arsenic-induced hepatopathy.

Diuretic action

Peppermint leaves

The effect of peppermint on diuresis is weak. The effective dose is about 30 times higher than that of aminophylline. At 1000 mg/kg oliguria was observed (Della logia et al, 1990).

Ginger

Zingiber officinale Roscoe, rhizoma

Ginger is the common name for the whole or cut rhizome (underground stems) of *Zingiber officinale*, a plant native to Southeast Asia. The plant is cultivated or gathered to obtain the rhizome for medicinal use.
The exact way ginger acts on the stomach and gut is not fully known, but it is thought to work by blocking certain receptors for the hormone 5HT3, known as serotonin, which are involved in the contraction of the smooth muscles inside the stomach and gut. When serotonin attaches to these receptors it causes nausea and vomiting.

In its assessment, the HMPC considered a number of clinical studies with ginger, looking at its effectiveness in treating different conditions. In particular, ginger has been compared with placebo (a dummy treatment) or other treatments in the prevention of nausea and vomiting in motion sickness. The results showed that ginger was more effective than placebo and as effective as other medicines in preventing motion sickness.

Ginger (Zingiberis rhizoma) consists of the whole or cut rhizome of *Zingiber officinale* Roscoe (*Zingiberaceae*), with the cork removed, either completely or from the wide flat surfaces only. Ginger plants have been extremely popular – for cooking as spice and to treat a host of ailments – throughout Asia, especially in India and China, for over 5000 years.
The species *Zingiber officinale* originates from Southeast Asia. It is not known to occur wild [Teuscher 2006; Langner *et al.* 1998; Germer *et al.* 1997]. It is a perennial herb, up to 1.5 metre in height, with asymmetric flowers. Due to the long period of breeding in different continents, different types of the species have developed. The herbal drug ginger, that complies with the monograph of the European Pharmacopoeia, originates from the West Indian type (Jamaica-ginger) with the cork removed or from Indian types (Bengal-ginger, Cochin-ginger) peeled on the flattened sides only.
Constituents: Volatile oil 1-4 % (Ph. Eur. min 15 ml/l). More than 100 compounds are identified, most of them terpenoids mainly sesquiterpenoids (α-zingiberene, βsesquiphellandrene, β-bisabolene, α-farnesene, *ar*-curcumene (zingiberol) and smaller amounts of monoterpenoids (camphene, β-phellandrene, cineole, geraniol, curcumene, citral, terpineol, borneol). The composition of the oil depends on the origin of the material [Afzal *et al* 2001; Ahmad *et al.* 2008; Ali *et al.* 2008; Chen & Ho 1988; Connell 1970; Erler *et al.* 1988; Lawrence 1984].
Experiments with rats have demonstrated a dose-dependent reversal of pyrogallolinduced (a free radical generator) delay in gastric emptying of oral ginger acetone extract (100, 250 and 500 mg/kg); however, ginger extract did not change gastric emptying in animals that were not pre-treated with pyrogallol [Gupta & Sharma 2001], and a study by the same group showed a partial reversal of the inhibitory effect of cisplatin on gastric emptying in rats by ginger acetone or ethanol extracts (in doses of 200 and 500 mg/kg orally) or ginger juice (2 and 4 ml/kg) [Sharma & Gupta 1998]. In the musk shrew, oral administration of acetone extract of ginger (150 mg/kg), 6-gingerol (25 mg/kg and 50 mg/kg) and metoclopramide (25 mg/kg) administered 60 minutes prior to cyclophosphamide provided complete protection from emetic episodes [Yamahara *et al.* 1989a]. Dried ginger extract (1 gram) stimulated contractile activity primarily in the gastric antrum in conscious dogs [Shibata *et al.* 1999] while an aqueous ginger extract administered over 6 days had no inhibitory activity on gastric emptying in mice in terms of the test meal weight in the stomach assessed at 20 minutes after giving the test meal [Chen *et al.* 2002].
One *in vitro* trial showed that ginger acetone extract as well as 6-, 8- and 10-gingerol were able to inhibit serotonin-induced contractions of the isolated guinea pig ileum and hypothesised that

they all act by blocking 5-hydroxytryptamin 3 (5-HT_3) receptors [Yamahara *et al.* 1989b]. Further, *in vitro* studies have demonstrated that ginger hexane extract and some of its active principles (6-gingerol, 8-gingerol, 10-gingerol and 6shogaol) are able to inhibit 5-HT_3 receptor function [Abdel-Aziz *et al.*2005; Abdel-Aziz *et al.* 2006]. Ghayur & Gilani [2005a] showed that methanolic ginger extract produced a dose-dependent (dose range 0.01-5.0 mg/ml) stimulant and then a spasmolytic effect in atropinized rat and mouse stomach fundus, and a dose-dependent (0.1-3.0 mg/ml) spasmolytic effect on rabbit jejunum, and rat, mouse and guinea pig ileum. Other *in vitro* studies have shown that ginger extract inhibited rat ileum smooth muscle activity provoked by electrical stimulation [Heimes *et al.* 2009], which was reduced by a vanilloid receptor antagonist suggesting pre-junctional vanilloid receptor involvement [Borelli *et al.* 2004].
In rats with postoperative ileus a single dosage of processed ginger root (150 mg/kg orally) did not affect the delayed gastrointestinal tract transit [Tokita *et al.* 2007].
In mice an acetone extract of ginger at 75 mg/kg, 6-shogaol at 2.5 mg/kg and 6-, 8- and 10-gingerol at dosages of 5 mg/kg significantly enhanced the transport of a charcoal meal [Yamahara *et al.* 1990]. In mice an aqueous ginger extract in an oral dosage of 150 mg/kg inhibited the accelerated small intestinal transit induced by carbacholin, an effect that was ascribed to shogaol [Hashimoto *et al.* 2002]. A methanolic ginger extract enhanced a charcoal meal travel (that was completely blocked by atropine pretreatment) through the small intestine in mice in dose-dependent (30 and 100 mg/kg) fashion [Ghayur & Gilani 2005a].
Ginger root may inhibit the induction of genes encoding cytokines and chemokines that are synthesised and secreted at sites of inflammation.

In vitro standardised extracts of ginger were reported to inhibit amyloid Aß peptide induced cytokine and chemokine expression in cultured THP-1 monocytes (a cell culture model of human microglial cells) [Grzanna *et al.* 2004]. In a murine macrophage cell line alcoholic ginger extract at a concentration of 100 μg/ml induced macrophage inducible nitric acid synthase mRNA expression and nitrogen oxide (NO) production [Imanishi *et al.* 2004], while in murine microglial cells ginger extract inhibited the LPS induced excessive production of NO (by down-regulating iNOS) and pro-inflammatory cytokines associated with suppression of NF-κB and mitogen activated protein kinase [Jung *et al.* 2009], and in human synoviocytes ginger extract suppressed cytokine production (associated with suppression of NF-κB and IκB-α activation) [Frondoza *et al.* 2004] and chemokine expression [Phan *et al.* 2005]. Treatment with processed ginger inhibited the up-regulation of cytokine induced neutrophil chemoattractant in monocrotaline induced sinusoidal obstruction syndrome in rat liver [Narita *et al.* 2009]. *In vitro* studies showed that fresh ginger in a dose-dependent fashion suppressed mitogen and alloantigen mediated lymphocyte proliferation [Wilasrusmee *et al.* 2002a] and interleukin-2 production from mixed lymphocyte culture [Wilarusmee *et al.* 2002b], and a study by Tripathi *et al.* [2008] suggested that the mechanism behind the inhibition of T-cell proliferation by ginger was suppression of the antigen presenting cell function of macrophages by down-regulating MHC class II molecule expression.

***Foeniculum vulgare* MILLER**

Foeniculum vulgare Mill. subsp. *vulgare* belongs to the *Apiaceae* (Umbelliferae) botanical family.
The material of interest for medicinal use is the dried fruit (i.e. whole cremocarp and mericarp). The European Pharmacopoeia describes two varieties: sweet (subsp. *dulce*) and bitter fennel fruit (subsp. *vulgare*)

Sweet fennel fruit consists of dry cremocarps and mericarps of *Foeniculum vulgare* Mill. subsp. *vulgare* var. *dulce* (Mill.) Batt. & Trab. and it is characterized by a content of essential oil not lower than 20 ml per kg anhydrous fruit with a 80.0% minimum content of anethole in its essential oil. Sweet fennel is pale green or pale yellowish-brown (Ph. Eur. 8th Edition 04/2011:0825).
Bitter fennel fruit consists of dry cremocarps and mericarps of *Foeniculum vulgare* Mill. ssp. *vulgare* var. *vulgare;* it contains not less than 40 ml per kg anhydrous fruit of essential oil that contains 60.0% not less than 80.0% of anethole and not less than 15.0% of fenchone. Bitter fennel is greenish-brown, brown or green (Ph. Eur. 8th Edition 04/2013:0824).
The fennel fruits also contain water-soluble glycosides of monoterpenoid, alkyl and aromatic compounds (Kitajima *et al*., 1998) as well as, among other substances, proteins, cellulose, lignin, pectins, triglycerides containing mainly petrosilinic, oleic and linoleic acids, wax esters, phospholipids, phytosterols (e.g. beta-sitosterol and stigmasterol), flavonoids, hydroxycoumarins, furanocoumarins and vitamins (tocopherol and tocotrienol) (Kunzemann and Herrmann, 1977; Zlatanov, 1994; Ivanov and Aitzetmuller, 1995; Reiter and Brandt, 1985; Council of Europe, 2002).
Compounds identified in essential oils obtained by steam distillation from ripe fruits of bitter and sweet fennels: *Trans*-anethole; Fenchone; Estragole; Alpha-pinene; Limonene; Alpha-pinene/Limonene; *Cis*-anethole, Anisaldehyde ; Beta-myrcene

For the symptomatic treatment of digestive upsets such as: epigastric distension, slow digestion, eructation, flatulence

Pharmacological studies

Addition of 0.5% of fennel to the diet of rats for 6 weeks shortened food transit time by 12% ($p<0.05$) (Platel and Srinivasan, 2001).

Fennel administered orally at 24 mg/kg b.w. increased spontaneous movement of the stomach in unanaesthetized rabbits and reduced the inhibition of stomach movement induced by sodium pentobarbitone (Niiho *et al*., 1977).
An aqueous extract of fennel (10% w/v), perfused through the stomach of anaesthetized rats 0.15 ml/minute and collected over periods of 20 minutes, significantly increased gastric acid secretion ($p<0.02$) to more than 3-fold compared to the basal secretion determined from perfusion of saline solution (Vasudevan *et al.*, 2000).

1. *Spasmolytic effect on contracted smooth muscles*

Fennel fruit alcoholic extracts and oil exerted a relaxing effect on *in vitro* pre-contracted smooth muscles from different organs (tracheal, ileal and uterine) by antagonizing several contraction-inducing agents.
A 30%-ethanolic extract from bitter fennel (1 part of drug to 3.5 part of ethanol 31% w/w) produced a concentration-dependent decrease in acetylcholine-and histamineinduced contractility of isolated guinea pig ileum at concentrations of 2.5-10 ml/litre; however, taking into account the effect of ethanol, only the results with histamine were significant ($p<0.005$ at 10 ml/litre) (Forster *et al*., 1980). In the same test system, the extract at 2.5 and 10 ml/litre also concentration-dependently reduced carbachol-induced contractility (Forster, 1983). Fennel essential oil was also reported, at a concentration of 10 mg/ml, to antagonize the action of acethylcoline, pilocarpine, physostigmine or of barium chloride on intestinal jejunum isolated from different animals (quoted by Teuscher at al., 2005).

Fennel essential oil cause primarily a relaxation (lasting from 5 to 30 minutes) of the walls and decrease in the peristaltic contractions of the stomach in unanesthetized dogs (5 to 25 ml of distillate administered to dogs by means of a catheter inserted into stomach or an intestinal fistula). In about half of the observations the relaxation and decrease in peristalsis was followed by some increase in tone or in amplitude of the contractions or both. In less than half of the tests where it could be observed, there was some increase in the activity of a loop of intestine when the fennel essential oil was placed in the stomach. When introduced into the colon, dilute solutions of fennel essential oil increase the tone and contractions, just as they do in the small intestine, but the effect lasts longer in the colon than it does in the ileum (Plant and Miller, 1926) (to be checked)

Fennel essential oil significantly and dose-dependently reduced the intensity of oxytocininduced contractions ($p<0.01$ at 50 μg/ml) and PGE_2-induced contractions ($p<0.01$ at 10 and 20 μg/ml) of the isolated rat uterus. The oil also reduced the frequency of contractions induced by PGE_2 (but not by oxytocin) (Ostad *et al*., 2001).

1. *Anti-inflammatory effect*

Oral pre-treatment of rats with a dry 80%-ethanolic extract from sweet fennel at 100 mg/kg b.w. inhibited carrageenan-induced paw oedema by 36% ($p<0.01$) compared to 45% inhibition by indometacin at 5 mg/kg (Mascolo *et al*., 1987).

General uses of constituents from Orexis combination

Valussi, M. Functional foods with digestion-enhancing properties International

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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.

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 Etkin NL, Ross PJ.

1994. Pharmacological implications of “wild” plants in Hausa diet. In: Etkin NL. editors. Eating on the wild side: the pharmacological, ecological, and social implications of using noncultigens. Tucson, AZ: The University of Arizona Press.; Balick and Cox Balick M, Cox L. 1996. Plants, people, and culture: the science of ethnobotany.
New York: Scientific American Library. Pieroni and Price 2006 Pieroni A, Price LL. 2006. Eating and healing: traditional food as medicineNew York: The Haworth Press.).

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:

1. 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 Pieroni A, Price LL. 2006. Eating and healing: traditional food as medicineNew York: The Haworth Press.

2. 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 Leonti M, Nebel S, Rivera D, Heinrich M. 2006..

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). Taste and health: nutritional and physiological significance of taste substances in daily foods: role played by afferent signals from olfactory, gustatory and gastrointestinal sensors in regulation of autonomic nerve activity.

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)

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

CSVDisplay Table

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). Epithelial cells and their neighbors. II. New perspectives on efferent signaling between brain, neuroendocrine cells, and gut epithelial cells. 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) .

Taste receptors in the gastrointestinal tract. IV. Functional implications of bitter taste receptors in gastrointestinal chemosensing.. Bitter receptor activation, mediated by CKK, seems to be aimed at reducing the absorption of the bitter compounds and at maximizing the absorption of complex carbohydrates, essential fatty acids and fatsoluble vitamins (Jeon et al. 2008)
Figure 2. The relationships between bitter receptors activation, gut peptide release, CNS activation and gastrointestinal effects.

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

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 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.
Dandelion (*Taraxacum officinale* G.H. Weber ex F. H. Wigg – Asteraceae) roots and leaves (cfr. Valussi 2011)) 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.

Fennel extracts

The fruits of Fennel (*F. vulgare* Mill. – Apiaceae) (cfr. Valussi 2011) 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 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 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.
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.

Peppermint extract

Peppermint (*Mentha xpiperita* L. – Lamiaceae) (cfr. Valussi 2011)) 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.

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.

Ginger extract

Ginger rhizome (*Zingiber officinale* Roscoe – Zingiberaceae) (cfr. Valussi 2011) 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.

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.

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.

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