Phytotherapy in Functional Gastrointestinal Disorders

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Abstract

Background: Phytotherapy is an important therapeutic option in functional gastrointestinal diseases (FGID). It has a large tradition, with different approaches in different regions of the world, some of which have made their way into modern evidence-based medicine (EBM). **Summary:** Taking into account the number of herbs in use, and also the cumulated scientific evidence on them, FGID are possibly the most important indication in phytotherapy. This does not only apply for European phytotherapy, but also for other regions, such as Asia. Within European phytotherapy, herbs active in FGID are usually classified according to their main active constituents and their activities. Typically, the herbs used in FGID are grouped into amara, aromatica, amara aromatica combining both properties, herbs stimulating gastric secretion, herbs containing spasmolytic and carminative essential oils or spasmolytic alkaloids, mucilaginous soothing the mucosa, and flavonoid containing drugs with anti-inflammatory properties. In phytotherapy, different plants are frequently combined to maximize effectiveness and specificity of action. Very potent combination products can be developed

when the mechanisms of action of the combination partners are complementary. This approach can be demonstrated by the example of STW 5. For this herbal combination product, therapeutic efficacy in FGID has been clinically proven according to the highest standards of EBM. This example also underlines that modern rational phytotherapy is definitely part of modern EBM. **Key Messages:** FGID is one of the most important indications in phytotherapy and rationally combined herbal preparations are established evidence-based therapeutic options.

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Use of Herbs in Functional Gastrointestinal Diseases

Judging by the historic medicinal literature, functional gastrointestinal diseases (FGID) have always been an issue in the history of mankind, and herbal preparations were regularly used for treatment. Examples can be found in the Egyptian “Papyrus Ebers” and the Chinese “Shén-nóng Běncǎo Jīng,” which both mention herbal remedies for gastrointestinal ailments. Modern compendia on medicinal herbs also contain a wealth of plants used in FGID, which can make up to 34% of all medicinal plants listed (Table 1).

Table 1. Online compendia of scientific bodies on medicinal plants. Number of plants mentioned for the treatment of functional gastrointestinal diseases (retrieved October 3, 2017)

Scientific body, database	Internet link	Key word defined in the compendium for functional gastrointestinal diseases	Total number of medicinal plants in the compendium	Number and percentage of medicinal plants for the treatment of gastrointestinal diseases, <i>n</i> (%)
ESCOP monographs App	www.escop.org	Dyspepsia, indigestion	101	17 (16.8)
Phytokodex (Austria)	http://www.kup.at/db/phytokodex	Dyspepsia, indigestion	217	52 (24.0)
Koop Phyto, herbal encyclopedia	www.herbal-encyclopedia.info	Gastro-intestinal diseases	184	48 (26.1)
HMPC of EMA	www.ema.europa.eu	Gastrointestinal disorders	141	48 (34.0)
American Botanical Council, HerbMedPro	www.herbalgram.org	Dyspepsia, irritable bowel syndrome	257	70 (27.2)

ESCOP, European Scientific Cooperative on Phyto medicines; Koop Phyto, Kooperation Phytopharmaka GbR; HMPC, Committee on Herbal Medicinal Products; EMA, European Medicines Agency.

Mode of Action and Therapeutic Use

Medicinal plants used in the treatment of FGID, as for example, acute functional dyspepsia (often accompanied by spasms), are typically perceived to have a rapid and reliable therapeutic effect. Moreover, the use of herbal medicinal preparations also covers the application in chronic or remittent gastric diseases. This therapeutic use has been documented in a systematic way in medical textbooks (e.g., [1–3]). Some of them, as those of Weiss and Madaus, have been first-time edited in the first half of the 20th century, laying the foundations for today's rational phytotherapy.

In these textbooks, the plants used in the treatment of digestive diseases are grouped in a pragmatic way according to their most prominent constituents and their pharmacological effects. In the textbook of Schilcher [4], the plants relevant in the treatment of FGID have been grouped as follows:

Amara

Amara are plants with a predominant content of bitter substances and a stimulating action on gastric secretion and gastrointestinal motility [5]. Bitter substances are a heterogeneous group of chemical compounds with the bitter taste as a common feature. Their effect is not only mediated via the mouth by bitter receptors [6], but they also have a direct effect on the stomach, leading to hyperemia of the mucosa, increased gastric secretion, and even

quicker gastric emptying [7]. Amara may also have additional effects, such as an increase of bile secretion. Examples:

Cnicus benedictus (St. Benedict's Thistle)

Cnicus benedictus is used as an amarum due to its content of bitter sesquiterpene lactones (cnicin), besides very small amounts of essential oil, supporting its use in stimulating gastric secretion.

Gentiana lutea (Yellow Gentian)

Gentian (as well as Common Centaury) is a prototypical amarum that contains bitter secoiridoid glycosides, such as amarogentin and gentiopicroside. Gentian stimulates the secretion of saliva and gastric acid, increases blood flow in the gastric and intestinal mucosa, improves the motility of the stomach, and is also used as a roborant and tonic.

Aromatica

Plants with a predominant content of essential oil with spasmolytic activity or stimulating effects on peristalsis. Essential oil (also called volatile oil) is a liquid mixture of solid or liquid compounds characterized by its volatility. Among their constituents are mono- and sesquiterpenes, alcohols, aldehydes, ketones, phenols, acids, esters, and ethers. They are quickly absorbed by the gastrointestinal mucosa and metabolized by conjugation with sugars. Examples:

Table 2. Herbal drugs available for the development of STW 5 and their most important properties [4, 15, 16], and herbal drugs factually selected for the development of STW 5

Plant	Tonicising	Spasmolytic	Antiphlogistic	Stimulation of acid secretion	Role and proportion, mL/100 mL within STW 5
Angelica		XX	X		Basic component, 10/100 mL
Artemisia	X			XX	Not used
Achillea		X	X	X	Not used
Acorus		X		XX	Not used
Silybum			X		Basic component, 10/100 mL
Cnicus				XX	Not used
Gentiana	X			XX	Not used
Carum	X	X			Basic component, 10/100 mL
Matricaria		X	XX		Main basic component, 20/100 mL
Mentha		XX		X	Adjuvant component, 5/100 mL
Melissa		X			Basic component, 10/100 mL
Atropa		XX			Not used, narrow therapeutic range
Chelidonium		X			Basic component, 10/100 mL
Potentilla		X			Not used
Erysimum	X				Not used, centrally cardioactive
Iberis	X		X		Main basic component, 15/100 mL
Glycyrrhiza		X	X		Basic component, 10/100 mL

X, XX, strength of action (arbitrary rating, modified from Schilcher [4]).

Carum carvi (Caraway)

The fruits of caraway, a member of the Apiaceae family, contain up to 7% essential oil with (S)-(+)-carvon and (R)-(+)-limonene as the major constituents. They are known to have spasmolytic and carminative effects, while also stimulating the tone of gastrointestinal smooth muscle and increasing mucus secretion.

Matricaria chamomilla (= *Chamomilla Recutita*, Chamomile)

The dried flower heads of this member of the Asteraceae family contain up to 1.5% of essential oil which is blue in color. The lead constituents chamazulene and (–)- α -bisabolol are involved in the antiphlogistic activity of the oil. Chamomile has both carminative and spasmolytic effects, making it one of the most useful medicinal herbs in acute gastric diseases. Besides essential oil, the flower heads also contain flavonoids, such as apigenin-7-glycoside, which contribute to the spasmolytic activity and may inhibit peristalsis. Chamomile is therefore used in painful gastrointestinal spasms as well as acute gastritis, ulcers, and dyspepsia.

Mentha piperita (Peppermint)

Peppermint leaves contain essential oil (menthol and menthone) and caffeic acid derivatives, such as rosmarinic acid. Other than chamomile, the spasmolytic activ-

ity is much more predominant, while an antiphlogistic effect is lacking. Therefore, the main indications are gastropathic states, including dyspeptic conditions.

Melissa officinalis (Lemon Balm)

Like peppermint, lemon balm also belongs to the Lamiaceae family. The leaves are used for medicinal purposes, as they contain up to 0.8% of essential oil with components such as citral, citronellal, linalool, geraniol, and β -caryophyllene, besides ca. 4% caffeic acid derivatives (rosmarinic acid). In the gastrointestinal tract, lemon balm has spasmolytic and carminative action, supporting its use in gastric malfunctions and spastic states of the gastrointestinal tract.

Amara-Aromatica

Plants with bitter substances as well as essential oils, which act spasmolytic and also stimulate gastrointestinal motility. They can also have an anti-inflammatory effect. Examples:

Achillea millefolium (Common Yarrow)

The herb contains bitter compounds and aromatic essential oil, and is therefore classified under “Amara aromatica.” It is used in gastric hyposecretion, gastritis, and dyspepsia, as it has antiphlogistic, carminative, and spasmolytic properties.

Acorus calamus (Calamus)

Calamus root contains 2–6% (sometimes up to 9%) of essential oil with bitter and hot taste. The roots, besides many other substances, also contain asarone, acorin, and tannins. They are used in chronic dyspepsia, hypoaacid stomach diseases, and in meteorism. Calamus also has spasmolytic and carminative effects.

Angelica archangelica (Angelica)

Angelica root contains up to 1.3% essential oil, as well as tannins, sitosterol, furocoumarin, and oxy coumarin derivatives, such as angelicin, and some acids. The drug is rated as an amarum aromaticum, the bitter taste being mainly based on the coumarins. The area of indications is broad, and in the field of gastric diseases it is mainly directed at gastropathia and dyspepsia, with carminative, spasmolytic and antiphlogistic effects.

Artemisia absinthium (Absinthe)

Absinthe contains about 1% essential oil and different bitter compounds, sesquiterpene lactones, for example, absinthin and artabsin. Its actions include tonicizing effects and a stimulating effect on bile and acid secretions. Its main indications are acute and chronic dyspepsia, but also constipation caused by hypomotility of the intestine.

In addition to amara and aromatics, 2 other groups of plants are of relevance in functional dyspepsia and irritable bowel syndrome. They are also characterized by typical phytochemical constituents:

Plants with Spasmolytic Alkaloids

This group of plants is comparatively small. Some of the alkaloids in the plants of this group are pharmacologically highly active. Two plants of this group are specifically mentioned here:

Atropa belladonna (Belladonna)

Among the alkaloids of this member of the Solanaceae family, hyoscyamine is the most important, next to scopolamine, apoatropine, and belladonnine. These compounds are ester alkaloids and pharmacologically very active, for example, hyoscyamine leads to central stimulation. In the digestive organs, belladonna reduces the tone, lowers excitation, and diminishes the gastric and intestinal motilities. Indications in gastrointestinal diseases are spastic constipation, gastralgias, pylorospasm, Ulcus ventriculi, intestinal spasms; in case of hyperacidic ulcers, the inhibition of gastric secretion is helpful.

Chelidonium majus (Greater Celandine)

Greater Celandine belongs to the Papaveraceae family and contains several alkaloids, such as chelidonine, sanguinarine, and α - and β -homochelidonine, which have pharmacologically well characterized spasmolytic and analgesic actions. The extract has analgesic properties and a good spasmolytic action on smooth muscle, for example, bronchial smooth muscle and intestine, and stimulates bile secretion. It is used in spastic states of the gastrointestinal tract.

Plants with Other Constituents

Not all plants used in FGID can be clearly allocated to the groups described above. Some of them are characterized by flavonoids that have a broad spectrum of relevant actions, such as spasmolytic, anti-inflammatory, and anti-oxidative properties. In addition, other characteristic constituents such as mustard oil glycosides or glycyrrhizic acid may be present. Examples:

Erysimum cheiri (Wallflower)

This plant from the Brassicaceae family was formerly called *Cheiranthus cheiri*. It contains mustard oil glycosides, for example, glucocheirolin, besides cardioactive components (cheirototoxin). It is therefore active in cardiovascular and hepatic indications.

Iberis amara (Bitter Candytuft)

Bitter Candytuft is also a member of the Brassicaceae family, and, like *Erysimum*, it contains mustard oil glycosides. In contrast to *Erysimum*, it does not have cardiovascular activities. Mustard oil glycosides are known to be tonicizing and antiphlogistic. Their action is supported by the presence of small amounts of cucurbitacins, bitter substances well known from the Cucurbitaceae (pumpkin) family. Flavonoids add to the anti-inflammatory action.

Glycyrrhiza glabra (Liquorice)

Liquorice is mainly known for its antiphlogistic and spasmolytic effects. Its most characteristic constituent is the fraction of glycyrrhizin derivatives, which are known for their sweet taste, as well as for their anti-inflammatory and mucosa-protective properties.

Potentilla anserina (Common Silverweed)

The plant is a member of the rose family and contains up to 10% tannins, flavonoids, and an as yet unknown compound with spasmolytic action. The effect can be demonstrated with intestinal spasms induced by barium chloride. It has been successfully used in meteorism, in-

testinal spasms, and pylorospasms. *Potentilla anserina* is less potent than belladonna and celandine, but may be beneficial in combinations.

Silybum marianum (Milk Thistle)

Milk thistle fruits contain bitter substances, with silymarin complex being the best-known constituent related to activity. In addition to their protective effects in hepatic diseases and liver-related intoxications, milk thistle fruits can have slight stimulating properties on gastric secretion and bile production.

These examples have been established in European phytotherapy since many decades. A broad body of evidence of their phytochemical composition, action, therapeutic experience, and partly also data from clinical trials are available [8].

Combining Herbal Substances in a Rational Background

As a general rule, the action of a single herb does not usually meet the requirements for the treatment of a complex condition, such as functional dyspepsia or irritable bowel syndrome. Typically, combinations of, for example, aromatic and bitter substances are used, often with components from other groups [9, 10]. The combination of herbal preparations is a typical feature within phytotherapy. Because of multi-drug – multi-target effects, a combined herbal preparation can be better suited to the medicinal needs and pharmaceutical preconditions of use than a preparation from any one of the single plants [11–13].

The textbook of Rudolf Fritz Weiss [2], one of the foundations of rational phytotherapy in Germany, advises to combine herbal preparations. It assigns different roles to the combination partners, such as the classification as basic, adjuvant, aromatizing, and stabilizing components. Additionally, Weiss stressed the importance that all components of a combination have a similar direction of action as the basic component. This advice was originally directed to the composition of herbal teas, but was also used in combining herbal tinctures in a strategic manner.

The Example of the Development of STW 5 as a Rational Herbal Combination Product

A number of herbal medicines were developed in Germany in the late 1950s and early 1960s, to address the expanding need for medicinal products during the phase

of economic recovery after the end of the Second World War. In parallel, there was an increasing focus on indications today termed as FGID, which at that time were described by various terms including gastritis and stomach complaints. Irritable bowel syndrome including diarrhea and constipation was already known as a defined disease.

The physiology of the gastrointestinal tract was understood in its main parts, and the main causes of gastrointestinal diseases and their interplay were well known, as for example the frequent occurrence of gastrointestinal muscle spasms in dyspeptic diseases and in acute gastritis, that is, inflammatory gastric complaints. The symptomatic consequences of gastric hypo- and hyper-secretion were also known. At the same time, a broad knowledge on many herbs was available in publications and textbooks mentioned above, for example, those of Madaus [1] from 1938 or Weiss [2] from 1944, which included information on many phytochemical constituents, the pharmacology and toxicology as well as the experience from their therapeutic use.

The rationale for the development of STW 5 is reflected in the newsletters published by its manufacturer, written by scientists involved in the development of its medicinal products. These newsletters give information on the intended indication of the product, and on the available knowledge on the phytochemical, pharmacological, and medicinal profiles of plants available for respective indications [14, 15]. Numerous products based on plants from the groups of the *Amara* and *Amara aromatica* were available, which addressed a reduced acid secretion in the stomach. However, therapies for the much more widespread motility-related functional gastrointestinal disturbances were lacking.

The objective of the development of STW 5 (trade name Iberogast®) has been expressed as follows: Iberogast acts as an anti-inflammatory, spasmolytic, which normalizes both liver and biliary disorders, often concomitant in stomach and intestinal disorders. The blood flow in the mucosa of the stomach is fostered and an increase of gastric secretion is avoided. Under its application, the subjective complaints improve fast [15].

No single plant would have been suitable for this intended indication. Therefore, the development of STW 5 was based on the specific selection and combination of plants suitable for addressing this indication, taking into account that stimulation of acid secretion by the selected extracts had to be avoided, while maintaining anti-inflammatory, tonicizing, and spasmolytic properties (Table 2).

Two of the available plants were chosen as the major components with an increased proportion within the

combination, both lacking a stimulatory action on gastric secretion. These are camomile (20/100 mL), which is known for its antiphlogistic and spasmolytic properties, and Iberis amara (15/100 mL), which contains mustard oil glycosides with tonicizing and antiphlogistic properties. The latter plant is processed as a fresh plant extract, as it was found that drying would lead to hydrolysis of the active constituents.

Other plants were chosen as basic components (10/100 mL), and again none of them has a stimulatory action on gastric secretion, but all are known to have antiphlogistic, spasmolytic or tonicizing effects. One further plant, peppermint, was chosen despite a slightly stimulatory action on gastric secretion, as peppermint has a very predominant spasmolytic action, and is therefore a potential adjuvant to the other plants, while a relevant prosecretory action is not to be expected in the small proportion as contained in STW 5 (5/100 mL).

The concentration of ethanol in the extraction solvent has an impact on the extractability of plant constituents of different polarities. By choosing 30% ethanol as the extraction solvent, polar components of the herbs such as flavonoids and plant acids, and also less polar components, such as essential oil constituents, can be extracted. In addition, this ethanol concentration is suitable to warrant the stability of the extracts. For the extraction of *Iberis amara*, ethanol 50% (v/v) is used, as this plant is used as a fresh plant and has a considerably high water content than dried herbal drugs. Using this approach, extracts with equal solvent characteristics can be achieved, and they can be easily combined and used in therapy without the need for further processing steps, potentially compromising quality and efficacy.

The decision for the composition of STW 5 was therefore the result of a deliberate deduction from the intended therapeutic indication and the properties of potentially useful herbs. The idea of avoiding stimulating properties with respect to acid secretion was aimed at the large group of patients, who today are subsumed under the indications “functional dyspepsia” and “irritable bowel syndrome” [4].

Contribution of the Components to the Clinical Effects

STW 5 and its components have been studied in more than 100 pharmacological models and more than 25 clinical trials and studies (see also the contributions of Allescher and of Holtmann in this issue [17–19]).

Pharmacological studies confirmed its spasmolytic and prokinetic influence on gastric and intestinal motilities, its anti-inflammatory action in all parts of the gastrointestinal tract, its inhibitory action on GI neural hypersensitivity and on enhanced acid secretion, and, last but not least, its beneficial influence on intestinal microbiota [18, 20, 21]. According to these observations, the combination addresses the main causes of functional dyspepsia and irritable bowel syndrome (see also the contribution of Stanghellini in this issue [22]).

Toxicological risks have been proven to be very low or missing by a full set of toxicological studies, according to all relevant guidelines for drug development [23]. This is also confirmed by pharmacovigilance data, which document a very high safety [24], with single case reports of allergic reactions due to pre-existing hypersensitivity to plants of the Asteraceae family. For other reports, there are more probable alternative causes, so that a causal relationship to STW 5 is unlikely. Overall, the incidence of reports in the approximately 78 million patients to date who have used the product is very low. With respect to the ethanol content of the pharmaceutical form, modern assessments confirm the lack of any relevant risk not only in adults, but also in children [25, 26]. The favorable benefit profile also includes elderly patients [27].

The efficacy has been proven by clinical studies according to the respective edition of the global Rome criteria. The results were subjected to several meta-analyses [27–30], which confirmed the rating of the evidence of the product to be highest class in terms of evidence-based medicine. As early as from 1999, STW 5 was included into the relevant German medical treatment guidelines [31, 32], and was most recently also included into the guidance publications of Rome IV on FGID [33].

Conclusions on Phytotherapy of Gastrointestinal Diseases

Phytotherapy has always been an important part in the therapy of gastrointestinal diseases, especially FGID. Herbs can be classified according to their major constituents and their action. This allows not only their use as single-herb preparations, but also as combinations. Combining herbs can lead to optimized targeting of the therapeutic indication, and hence to better treatment. The development of STW 5 is an example of the validity of this approach: Not only could the contribution of the single components to the overall treatment effect be

demonstrated in pharmacological models, but also the clinical efficacy has been proven according to the most recent standards of evidence-based medicine. This example underlines that evidence-based phytotherapy in gastrointestinal diseases is possible and beneficial for the patient.

Disclosure Statement

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