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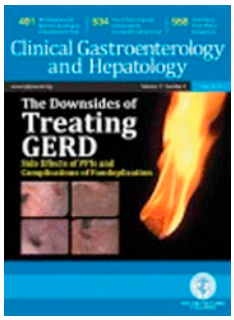

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Gerald Holtmann, Nicholas J. Talley

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Herbal medicines for the treatment of functional and inflammatory bowel disorders

Gerald Holtmann[1] * Nicholas J Talley[2]

[1]Department of Gastroenterology & Hepatology, Princess Alexandra Hospital Brisbane, & Faculty of Health Sciences, University of Queensland, Australia

[2] Faculty of Health & Medicine, University of Newcastle, Newcastle, NSW, Australia

Address for correspondence

Nicholas J. Talley MD, PhD, FRACP

Pro Vice-Chancellor and Dean of Health and Medicine,

and Professor of Medicine

University of Newcastle

Faculty of Health & Medicine

Callaghan, NSW, 2308, Australia

Abbreviations:

IBS – irritable bowel syndrome

FD – functional dyspepsia

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Author contribution

Prof. Talley- acquisition and interpretation of data, drafting and critical review of the manuscript.

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Abstract:

Herbal treatments have a long standing tradition for a range of gastrointestinal conditions. In contrast, the scientific evidence for the use of herbal preparations is mixed. Available studies are plagued by methodological limitations. For functional gastrointestinal disorders there is evidence for the use of some well characterized preparations. In inflammatory bowel disease (IBD) there are limited placebo controlled trials, other studies use active controls with suboptimal doses of the comparators.

Aside from patchy evidence supporting the use of herbal medicines, it is also of importance to consider that plants and plant extracts contain constituents that may vary depending upon environmental conditions during growth. Variable environmental conditions may affect the composition and the concentration of the active ingredients. In addition, most herbs provide a variable plethora of chemical families with medicinal utility. While these ingredients might be of benefit, the concentration and dose of these constituents needs to be closely monitored. Nevertheless, many herbal preparations are marketed without evidence for stringent adherence to good manufacturing practice (GMP) guidelines. Thus physicians and regulators should be very cautious with the use of these remedies. Appropriate scientific evidence for the claimed clinical benefits should become mandatory. In addition, the standards for production and safety monitoring should comply with established standards for chemically defined products. With these processes in mind the full value of herbal remedies may come to light particularly as the bioactive compounds present in these preparations become recognized.

Keywords:

Herbal medicine; irritable bowel syndrome; functional dyspepsia; gastrointestinal

INTRODUCTION

Herbal remedies are widely used for a variety of gastrointestinal and non gastrointestinal disorders. This is reflected by a growing number of publications in this field (Figure 1). A recent Cochrane review reported the prevalence of complementary and alternative medicine (CAM) usage for countries in the European Community ranges between 0.3 and 86%.[1] Dissatisfaction with conventional therapies appeared to be the most common reason for CAM use.[1]

A survey in patients with inflammatory bowel disease (IBD) conducted in Italy observed that out of a cohort of 705 patients, 126 had used herbal or complementary therapies[2]. The majority of these patients did not experience an improvement of symptoms as the result of the alternative therapies. A Canadian study[3] involving 150 IBD patients reported use of CAM therapies by 60% of patients. This included 31% relying on exercise, diet, and prayer; this latter group was more likely to be older and female. However it is noteworthy that complementary treatments were predominantly used for symptoms such as pain/cramps (64%), diarrhea (60%), and gas/bloating (21%). Those using alternative therapies were not characterised by more intense health care utilisation, but had experienced insufficient symptom relief utilising chemically defined therapies. Comparing use in various countries, it appears that use was greater among North American patients than European patients.[4]

History of herbs and disease

Herbal medicine can be considered to be part of the oldest form of healthcare and herbal treatments have been used by all cultures throughout history. The medicinal use of plants has developed through observation and by trial and error. Herbals contain a variety of chemical substances that act upon the body. Many drugs commonly used today are of herbal origin. Interestingly the physician/scientist credited with bringing digitalis into mainstream medicine is William Withering who observed that digitalis from the foxglove plant was used by herbalists for the treatment of dropsy and heart disease. [5] Even the newer antimalarial drugs were developed from the discovery and isolation of artemisinin from the Artemisia annua plant which has been systematically used in China for almost 2000 years[6]. While knowledge about herbal therapies was initially passed by word-of-mouth this knowledge was first documented in 1200 BC during the late Shang dynasty[7].

The effects of herbal medicine for a variety of conditions was used and studied in the middle ages by benectine monks (i.e. Codex Bambergensis Medicinalis**).**[8] Other famous work was done by Benedictine abbott Walafrid Strabo (Liber de Cultura hortum) published long before

print was invented.[9] A similar collection of information is the Speyer Herbal book which is believed to be authored by Hildegrad von Bingen.[10]

Although many flowers and aromatic plants were grown for decorative purposes, other plants such as rosemary, aniseed, caraway, cumin, coriander, fennel laurel and mustard were cultivated in the herbal gardens of the monasteries and were used in the kitchens or pharmacies of these monasteries. It is interesting to note that the School of Medicine at Salerno in Southern Italy was in close contact with the nearby monastery of Monte Cassino. At that time the 'Antidotarium Nicolai Salernitani', written about 1100 was a remarkable collection of herbal recipes that were used by physicians. In the first version it contained 60 formulae. [11]

The German Benedictine nun Saint Hildegard of Bingen (1089-1179) authored two volumes of medical books, namely 'Liber Simplicis Medicinae' (The Book of Simple Medicine) and 'Liber Composite Medicinae' (The Book of Compound Medicine). These books contained detailed observations and recommendations on the effects of herbals and their therapeutic effects. This knowledge was acquired in part through experience in the gardens of nun's convents. St. Hildegarde herself was a member and later mother superior of the Disibodenberg community near Bingen in the Rhine Valley.[12]

Challenges with herbal medicines

It is evident that while experience and systematic observation had provided the platform to formulate treatment recommendations using herbals, it must be recognised that the underlying pathophysiologic concepts or pharmacologic modes of action were not known. Modern evidence based medicine targets well defined disease mechanisms with highly standardized synthetic medicines. To a large degree this has replaced herbal medicines. The advantages are evident. Optimal doses of pharmacological active ingredients can be administered, potential ingredients of herbal mixtures that may cause adverse events are eliminated and the activity or concentration (dose) of the treatment is not influenced by metereological variation (e.g. sun exposure), the seasons, or the physical composition of the soil in which plants are grown.

On the other hand, in many Asian and African countries, large proportions of the population depend on traditional medicine for primary health care. Interestingly, herbal medicines are the most lucrative form of traditional medicine, generating billions of dollars in revenue and are used to treat a large variety of conditions.[13]However in context the medical costs for

ulcerative colitis alone in the US in 1990 were estimated to be $0.4-0.6 billion and this does not inlcude the more expensive biological therapies that are commonly used today. [14]While herbal medicines have a long tradition, there are significant challenges to overcome when they are used as routine treatments. In the evidence based medicine environment, it is at least desirable that the treatment is based upon accepted pathophysiologic concepts. However, it must be acknowledged that for some conditions pathophysiologic concepts are not well established for each individual that receives treatment. The other challenge is that clinical efficacy should be established. Thus properly designed, randomized placebo controlled trials need to support the assumption that the treatment actually improves the disease or the symptom that is targeted.

Another key issue is the quality of the manufacturing process and standardisation of herbal medicines. These medicines are derived from plants that are grown in soils of variable quality and under diverse environmental influences, (temperature, hours of sunshine, humidity), that can have substantial effects on the active ingredients. In addition, variations in species of plants also needs to be considered. While the monks and nuns attempted to standardize environmental conditions for their plants by using protected monastery gardens in which to grow their herbs, this is not a solution for the industrial production of large quantities of herbal medicines. Good Agricultural Practices (GAP) recommend production and farm level approaches to ensure the raw materials used for herbal preparations are safe and without contamination or huge fluctuations in active ingredients, are not easy to achieve. For this reason, long standing supply arrangements between farmers producing herbals and pharmaceutical companies producing herbal medicines frequently occur. With these arrangements manufacturers aim to standardize the quality of the plant raw material used in production. This is clearly a different approach compared to the purchase of raw materials originating from a variety of producers from different geographic regions with potentially differing concentrations of active ingredients.

Plants and plant extract contain constituents synthesized during plant growth under various environmental stresses, providing a plethora of chemical families with medicinal utility. Thus another challenge is the standardization of extraction of the active ingredients. While there are established standards such as the European Pharmacopoeia (Ph Eur), in-house specifications that are based upon extract constituents and chemical properties may influence the characteristics and properties of a given herbal preparation. Thus, besides the origin, production and harvesting conditions of the plant, there are multiple factors that potentially influence the quality and ultimately the efficacy of a herbal medicine. There are sometimes concerns of bioequivalence of chemically defined drugs from different

manufacturers or sources, but the challenge of bioequivalence is even more important for herbal medicines.

Standardized extraction conditions may be applied and relevant quality parameters monitored such as drug-to-extract ratio (DER), the quality of the herbal drug (water content, content of extractable substances), the extraction solvent (concentration, time flow) and the procedure conditions (time, temperature, pressure). These all play a part in defining product quality.[15-18] These parameters need to be well defined and standardized to ensure quality standards of the product.

While chemically defined treatments target defined pathophysiologies, not all conditions and diseases have as yet comprehensively defined pathophysiological mechanisms that can be cured with a short term pharmacologic intervention. In gastroenterology, functional gastrointestinal disorders fit into this category.

Complementary and Alternative Medicine

CAM is widely used in the general population and in patients with chronic disorders such as inflammatory bowel disease.[4,19] On the other hand, the efficacy of chemically defined drugs is limited in the treatment of patients with functional gastrointestinal disorders. As a consequence there is an unmet treatment need for treatment to manage patients with irritable bowel syndrome (IBS) and functional dyspepsia, and for many years herbal medications have been used in many countries for this purpose. A google search of the term “herbal treatment for dyspepsia” revealed more than 1 millions hits. This compared to 1.7 million hits for “PPI treatment for reflux” . There has been a steady increase in publications for complementary and alternative and herbal medicine over the past 30 years (Figure 1).

Herbal treatments for functional gastrointestinal disorders

There are a number of clinical trials focussing on the effects of herbal medicines in patients with functional dyspepsia [20-34] (Table 2) and IBS [35-37,40-41] (table 3). Most studies suggest efficacy of these herbal preparations. However, not all outcome parameters were assessed utilising validated instruments and blinding of herbal preparations is a critical problem of virtually all herbal trials. However it is important to note that in a matched-pair study a higher quality of placebo-controlled trials was shown for herbal medicines compared with conventional medicine. [38]

Overall, compared to chemically defined treatments, the number of trials focusing on functional dyspepsia and IBS is limited. One meta-analysis assessed the evidence for xiaoyao san (MXS) for treating functional dyspepsia (FD). The total effective rate of symptom improvement in this study for MXS ranged from 82.6% to 93.7%. Furthermore symptoms were reduced by a combination of MXS and prokinetic drugs compared to prokinetic drugs alone (odds ratio 4.32, 95% CI 2.64 to 7.08). However, there was evidence for publication bias and methodological flaws, which may have amplified the therapeutic benefit of MXS. [39]

Another study assessed a fixed combination of peppermint oil (90 mg) and caraway oil (50 mg) in a cohort of less than 50 patients with functional dyspepsia and found that this resulted in significant improvement of symptoms compared to placebo. [31]Placebo-controlled trials (Table 2) have reported significant improvement of symptoms in functional dyspepsia during treatment with specific herbal preparations [20-24, 26-28,30-33] One study showed a significant improvement in FD symptoms with chios mastic gum over placebo.[25] Another study showed improvement in FD and psychological symptoms with xinwei decoction compared with domperidone and placebo.[23] Artichoke leaf extract has been shown to improve FD symptoms and quality of life. [33] The results from studies in IBS (Table 2) however have been more mixed. [35-37]

A meta-analysis has also shown that supplementation of peppermint oil, in addition to pharmacological standard treatments, was of benefit to both constipation predominant IBS and diarrhea predominant IBS patients.[42] Another study showed a significant long lasting improvement of Chinese herbal medicine (standardized and individualised) compared to placebo in IBS. [36] However one study utilising traditional Chinese medicine extracts from 11 herbs failed to find a global improvement in symptoms in patients with diarrhea predominant IBS over placebo. [41]It could be that the use of extracts rather than raw herbs may account for this descrepancy with some unknown yet important component being lost in the water extraction process. Also the placebo in this study did contain a very small amount of lactose. Others have found no therapeutic benefit of curcuma xanthorriza or fumaria officinalis over placebo in the treatment of IBS related pain or distension.[40]

Major problems of alternative medicines are related to a lack of standardization of the compounds, the inclusion of multiple potentially active extracts, and lack of knowledge about their long-term safety and precise mechanisms of action.[43] Use of herbal medicine should be restricted to compounds that have been properly tested according to Good Clinical Practice (GCP) guidelines and are produced according to GMP standards. Several clinical

trials are available for the herbal preparation STW5. This preparation contains extracts from bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, angelica root, celandine herbs, milk thistle fruit and is produced according to GMP standards and was tested in several clinical trials and has been shown to be superior to placebo in the treatment of functional dyspepsia.[44] The use of STW5 has also been found to be effective over placebo in the treatment of IBS symptoms. [35]

Mechanistic studies

While some data in relation to clinical efficacy and some in vitro studies exist, very little work has been done to characterize effects of herbal medicines in humans. As shown in table 1 one clinical study [45] observed an increased in the motility index of antral pressure waves in the first 60 minutes after administration of STW5. However, retention of liquids in the stomach was slightly increased but there was no effect on gastric emptying of solids or intragastric distribution. Other effects may relate to a modulation of the gastrointestinal microbiome. Although this has not yet been systematically studied, aloe vera appears to promote the growth of Lactobacilli such as L. acidophilus, L. plantarum and L. casei [46]

Herbal treatments for inflammatory bowel disease (IBD)

Many herbal preparations have immunomodulatory effects. [47-57] Thus it appears reasonable to trial herbal medications in patients with IBD. On the other hand, good, large clinical trials testing the effects of herbal therapy in IBD are widely lacking. In a very small randomised placebo controlled study in patients with mild to moderate active ulcerative colitis, sigmoidoscopic scores and laboratory variables showed no significant differences between aloe vera and placebo. However, clinical remission, or improvement and response of symptoms occurred in 30%, 37% and 47%, of 30 patients randomised to receive aloe vera compared to 7% ($P<0.1$), 7% ([$P<0.06$) and 14% ($P < 0.05$), of 14 patients taking placebo.[58]

Curmarin is a member of the ginger family (Zingiberaceae). The curcuminoids are natural phenols that are responsible for the yellow color of turmeric. A recent Cochrane analysis reviewed the existing analyses and found that only one trial fulfilled the entry criteria. [59]In the curcumin group 22% relapsed compared to 32% in the control group ($P = 0.31$). However it was noted that the endoscopic appearance of the mucosa at six months was significantly better in the curcumin group than in the control group. The authors of the Cochrane review concluded that curcumin may be a safe and effective therapy for maintenance of remission, but more data are required.

A herbal treatment with myrrh, dry extract of chamomile flowers and coffee charcoal has anti-inflammatory and antidiarrheal potential. In a randomised trial with a study population of less than 100, no inferiority with regard to the ability to maintain remission for this mixed preparation compared to the gold standard therapy mesalazine, was found. [60] The study showed that 22 patients treated with mesalizine experienced a relapse compared to 25 treated with the herbal preparation. It needs to be noted that the gain over placebo is usually less than 20% with mesalazine [61] and typical studies recruited several hundred patients to demonstrate a significant difference. In addition, well controlled studies demonstrate that higher doses (e.g. mesalazine 3.0 g OD are superior to the 0.5 g tid) are significantly better compared to 3 x 0.5 tid.[62] While traditional medicines such as oral 5-aminosalicylic acid drugs, oral corticosteroids and particularly the recent emergence of biological therapies have been found to be effective in inducing remission in IBD patients, these treatments have also been associated with varying cost effectiveness outcomes.[63] Thus, future research studies should also seek to compare the cost effectivness of herbal preparations to the newer chemically defined approaches for the treatment of IBD.

Adverse events related to herbal medicines

It needs to be noted that there are numerous case reports on adverse events related to herbal medicines. [64-67] These adverse events range from allergic reactions, [68-69] gastrointestinal side effects, [70] acute hepatitis [71] or other serious adverse events including Stevens-Johnson syndrome, anaphylactic shock and exfoliative dermatitis including reactions that may necessitate hospital admissions. [72] There have also been reports of hepatotoxicity. A critical review by Teschke et al. [73] revealed that many different herbs and herbal products have been implicated to cause toxic liver disease, however significant issues with the quality of these studies renders it difficult to determine whether the herbs were actually causal. Unlike other medications most herbal preparations are not regulated by the same legal and regulatory framework that applies for other medications and as such there is no mandatory reporting of adverse events. As a consequence only a very small proportion of adverse events might be recognised. Indeed, in a study conducted in the UK, more than 500 herbalists of the UK Register of Chinese Herbal Medicine were invited to participate in a study where each were to approach 10 consecutive patients and recruit them for participation. After informed consent, patients had to complete a baseline survey. After 4 weeks patients received a follow-up questionnaire which assessed adverse events potentially related to the Chinese herbal medicine during the 4 week treatment. Only 71 out of 700 herbalists agreed to participate and in total 194 patients returned baseline

questionnaires. 144 (74%) patients completed the 4-week follow-up questionnaires. 20 of the 144 patients (14%) reported 32 adverse events associated with Chinese herbal medicine over the 4-week period. However, in this survey no serious adverse events were reported. [74] It is important to note that the available published information strongly suggests that safety of herbal medicines cannot be taken for granted. They should be regulated in a similar way as chemically defined over-the-counter drugs.

Conclusions

Herbal medicines are widely used, predominately as over the counter preparations. The main driver for the use of herbal and complementary medicines is the unmet need of patients. This is in particular evident for functional gastrointestinal disorders. While there is relatively solid evidence for some herbal preparations, many trials conducted in this field have substantial methodological deficiencies such as sample sizes, blinding and assessment of outcome parameters.

On the other hand it must be acknowledged that most preparations tested are not patentable drugs and therefore the financial return of investments into clinical trials utilising widely used herbal preparations is very unlikely. As a consequence there is limited investment of producer and distributors of herbal medicines to further explore efficacy and safety of herbal medicines. It must also be acknowledged that the effect of herbal medicines may not simply result from the combination of various known active ingredients, but the effect of as yet unrecognised biologically active components of a particular herbal preparation. Due to the complexity of chemical components and potential actions, a comprehensive understanding of herbal drugs remains a challenge. To address this, research in this field requires a comprehensive systems approach in order to identify active ingredients and their targets. [81] The widespread notion that herbal therapies are non-effective but safe might not be correct. Herbal medicines contain multiple active ingredients that have the potential to be beneficial (or harmful) for a number of medical conditions. At the same time herbal medicines have the potential of significant adverse effects. This might be particularly relevant if herbal preparations are not produced under closely monitored conditions and post marketing safety surveillance conducted in a rigorous manner that is well established for chemically defined medications. Thus, therapies utilising herbal medicines should consider risk benefit analysis and it may be a matter of time for some herbal treatments until more evidence for their use is available.

Figure 1: There has been a steady increase in publications for complementary and alternative and herbal medicine over the past 30 years Publications with the key words “Complementary Alternative Medicine” or ”Herbal” were used and compared with the term “Evidence Based Medicine”.

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Table 1: *In vivo* effects of plant extracts on gastrointestinal motor and secretory function

Plant	***Effects gastrointestinal on motility***	***Secretory effects***	***Other properties***	***Clinical trials***	***References***
Angelica (***Angelica Archangelica)***	Dose-dependent enhancement of gastrointestinal tract motility in mice when compared with the negative control.[77]		Cytoprotective effect against cyclophosphamide of stem cells and intestinal tissues [77]		*76-77*
Artichoke (Cynara scolymus)	*Spasmolytic effect [78]*	Choleretic and anti-cholestatic effects as well as inhibiting actions on cholesterol biosynthesis and LDL oxidation [79]	Potential prebiotic effect [80]		*78-80*
Bitter candy tuft (Iberis amara)	Stimulatory effect on smooth muscles of the stomach and small intestine [87-82]	Acid secretion and leucotriene-concentration, reduced [83]	Dose-dependent antiulcerogenic effect (indomethacin-induced ulcer). Acid secretion and leucotriene-concentration, reduced while prostaglandin E2 content, increased. [83]	*As component of STW5 [29]*	*29, 81-83*
Caraway	In humans significant			*In placebo controlled*	*84-85*

(Carum carvi)	reductions of contraction antral and intestinal amplitudes [84]			*trial in combination with peppermint oil improvement of symptoms in functional dyspepsia* [85]	
Celandine (Chelidonium majus)			*Anti-infective properties* [86]		*86*
Chamonmile ***(***Chamomilla recutita) Matricariarecutita	Antispasmodic effect due to an inhibitory effect on Ca(2+) influx through the membrane of jejunal smooth muscle cells. [87]		*Antidepressive and anxiolytic effects.* [88]		*87-88*
Lemon balm ***(****Melissa officinalis)*			*Anxiolytic effects*[89] Cytotoxicity assays showed a significant protection of a 10 mug/ml dose of Melissa against hypoxia in cultured neurons [90] Melissa extract demonstrated a high virucidal activity against herpes simplex [91]		*89-92*

			M. officinalis aqueous extract possesses potent antioxidative properties [92]		
Peppermint oil *(Mentha x piperita)*	Inhibition of gastric motility index [93] Inhibition of duodenal motility [94] Peppermint oil improves the manometric features of diffuse esophageal spasm. No effect on LES [95]				*93-95*

Table 2: Clinical trials in functional dyspepsia (FD) utilising herbal medicines

Author	Disease	Treatment	Study design	End point	Sample size	Sign.
Zhang et al [20]	Functional dyspepsia (FD) of Spleen-deficiency and qi-stagnation syndrome	Chinese herbal medicine (CHM) Gastrosis No.1	multi-center, double-blind, placebo-controlled	Symptom score, after 4 and 8 weeks	162, 2:1 randomization	P<0.01
Zhao et al [21]	Functional dyspepsia cold and heat in complexity syndrome	Chinese herbal medicine Ban xia xie xin decoction	randomized, double-blind, placebo-controlled multicenter trial	Dyspepsia symptom score	101, 2:1 randomisation	P<0.01
Zhang [22]	FD of spleen-deficiency and qi-stagnation syndrome	Chinese herbal medicine LiuJunZi decoction	randomized, double-blind, placebo-controlled multicenter trial	Primary: Dyspepsia symptom scale, 2,4,8 weeks, Secondary: emptying of radiopaque barium markers	160, 2:1 randomization	Symptoms: ($P < 0.01$)., Gastric emptying: ($P < 0.05$).
Arai et al [23]	Functional dyspepsia	Rikkunshito vs. domperidone	paralleled, randomized controlled trial	Primary: Dyspepsia symptom rating scale (GSRS), 4	27, 1:1 randomization	Significant improvement of symptoms in both groups, correlation of symptom

				weeks, Secondary: of acylated ghrelin (AG)		improvement with change of AG
Wu et al [24]	FD of spleen-deficiency and qi-stagnation syndrome.	Two kinds of Zhizhu pills, one contains immature orange fruit of Citrus aurantium L.(IFCA) and the other contains that of Citrus sinensis Osbeck	randomized, group sequential, double-blinded, multicenter trial	Symptom score	163, cross over, randomised	Zhizhu pills containing IFCA significantly superior
Dabos et al [25]	FD, Rome II criteria	Chios mastic gum	Randomised parallel group, placebo controlled	Symptom score and patients global assessment	148, 1:1 randomisation	Marked in 77% of patients with active compared to 40% with placebo, p<0.05
Braden B et al [26]	FD Rome II	Stw5 vs. placebo	Randomized, double blind placebo controlled	Symptoms and gastric emptying	103, 1:1 randomisation	Improvement of symptom score (GIS) P<0.08 vs.placebo, Larger proportion of patients responder with Stw5 (p<0.05)
Van Armin et al [27]	FD Rome II	STW5 vs Placebo	Randomized, double blind placebo controlled	Symptoms (GIS)	315, 1:1 randomization	Active therapy significantly better (p<0.05) after 8 weeks

Zhao & Gan [28]	Functional dyspepsia accompanied with depression and anxiety	Xinwei Decoction vs. domperidone vs. placebo	Parallel group design	FD symptoms and anxiety & depression scale (HADS)	73, 1:1:1	Dyspepsia symptoms: Xinwei Decoction vs placebo and domperidone P<0.05,
Freise et al [32]	Functional dyspepsia and IBS	enteric coated capsule containing 90 mg peppermint oil and 50 mg caraway oil vs enteric soluble formulation containing 36 mg peppermint oil and 20 mg caraway oil was used as the reference	Parallel group design	Symptom improvement	213, 1:1 randomisation	Lower pain frequency in the enteric coated high dose group.
Holtmann et al [33]	Functional dyspepsia, Rome II	artichoke leaf extract vs placebo	Randomized, double blind, paralleled group	Quality of life (QOL) assessed by the Nepean Dyspepsia Index (NDI).	244	Active significantly better (p<0.05)
Madisch et al [29]	Functional dyspepsia Rome II	STW5 vs placebo	Randomised double blind parallel group,	GIS score	120 patients 4 treatments groups with cross over after 4 weeks	STW5 significantly (p<0.05) superior to placebo
Holtmann et al [34]	Functional dyspepsia	fixed peppermint oil/caraway oil	Randomised double blind parallel	Symptom score	120 patients	Peppermint/caraway significantly (p<0.05) superior as

		vs placebo	group,			compared to placebo
Rösch et al [30]	Functional dyspepsia	STW5 vs cisapride	Randomised double blind	GIS score	137 patients	No significant difference
May et al [31]	Non ulcer dyspepsia	fixed peppermint oil/caraway oil vs placebo	Randomised double blind	change in the intensity of pain and the global clinical impression	45 patients	Both endpoint significantly improved

Table 3: Clinical trials in irritable bowel syndrome (IBS) utilising herbal medicines

Author	Disease	Treatment	Study design	End point	Sample size	Sign.
Madisch et al [35]	IBS, Rome II	STW 5 (n = 51), research herbal preparation STW 5-II (n = 52), bitter candytuft mono-extract (n = 53) or placebo (n = 52).	Randomised double blind	changes in total abdominal pain and irritable bowel syndrome symptom scores	N=207, 1:1:1:1	STW 5 ands research preparation STW 5-II superior to placebo and candytuft mono-extract
Bensoussan et al [36]	IBS	Chinese herbal medicine (standard and individualized CHM) placebo	Random treatment allocation	Symptom improvement	113, 1:1:1	Significant improvement during active as compared to placebo. Individualised therapy had long lasting effects
Brinkhaus et al [40]	IBS	Curcuma xanthorriza, fumaria officinalis, placebo	Random double blind, placebo controlled	Global patient rating of IBS related pain and distension	106	No therapeutic benefit over placebo for IBS pain (P=0.81). IBS distension P=0.48)
Leung et al [41]	Rome II IBS – diarrhea predominant	Traditional medical extracts – 11 herbs	Random double blind, placebo controlled	Global symptom assessment	119	No global improvement over placebo P=0.38
Merat et al [37]	IBS	Colpermin (peppermint	Random double blind,	IBS symptom improvement	90	Abdominal pain improvement

		oil)	placebo controlled			(p<0.0001)