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A Review of the Mechanisms of Action of the Herbal Medicine, STW 5-II, Underlying Its Efficacy in Disorders of Gut–Brain Interaction

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ABSTRACT

Background: Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are disorders of gut–brain interaction (DGBIs). Patients with these disorders experience abdominal symptoms, frequently in relation to meal intake, and often are treated using pharmacological approaches that offer limited symptom relief. In addition to various pharmacotherapies, established treatment options include lifestyle modifications (such as diet) and, in certain patients, psychological interventions. Because of the limitations of the currently available treatments, many patients look for alternative options, including herbal preparations.

Purpose: In this review, we summarize the preclinical and clinical evidence informing the use of the herbal preparation, STW 5-II, for the treatment of patients with FD and IBS. Data from clinical trials provide evidence that STW 5-II is superior to placebo in offering symptom relief. Moreover, a substantial body of preclinical data on the mechanisms of action of STW 5-II suggests that its ingredients target multiple mechanisms relevant to pathophysiology and symptom generation that may underlie its beneficial clinical effects in patients with DGBIs.

1 | Introduction

Patients with disorders of gut–brain interaction (DGBIs), previously referred to as "functional gastrointestinal disorders", present with heterogeneous abnormalities in gut function, including motility dysfunctions, hypersensitivity to intraluminal stimuli, low-grade inflammation, altered intestinal permeability, gut immune activation, and imbalances in the upper or lower gut microbiome [1]. Stress in adulthood or early life has also been shown to be a significant risk factor for the emergence of chronic visceral pain in DGBIs and is often comorbid with other mood and anxiety disorders [1]. Established treatment approaches include a range of lifestyle modifications (e.g., dietary changes, stress reduction and physical exercise),

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Summary

- A key feature of functional dyspepsia (FD) and irritable bowel syndrome (IBS) is their multifactorial causes, associated with a broad spectrum of symptoms reflecting dysfunctions at various levels of the gut–brain axis. The multifaceted pathophysiology includes altered motility and secretion, autonomic nerve sensitivity and mucosal responses to sensory signals, impaired epithelial barrier function, inflammation, postinfectious manifestation of altered gastrointestinal functions, and gut dysbiosis. The effective treatment of these disorders remains a challenge.
- The phytomedicine, STW 5-II (Iberogast ADVANCE), containing extracts from *Iberis amara* (bitter candy tuft), *Matricariae flos* (chamomile flower, from *Matricaria chamomilla*), *Carvi fructus* (caraway fruit, from *Carum carvi*), *Melissae folium* (lemon balm leaf, from *Melissa officinalis*), *Menthae piperitae folium* (peppermint leaf, from *Mentha* × *piperita*), and *Liquiritiae radix* (liquorice root, from *Glycyrrhiza glabra*), represents a multi-targeted approach, addressing all relevant known pathophysiologies.
- Clinical studies have shown beneficial effects of STW 5-II for symptom relief, which is likely due to its multiple modes of actions.

pharmacotherapies, and psychotherapeutic interventions. However, because of the limitations of these established treatment modalities, many patients opt for alternatives, which include herbal medicines.

The phytomedicine, STW 5 (Iberogast Classic), has been used clinically to treat upper GI disorders for over six decades. STW 5 is a blend of nine hydroalcoholic (31% alcohol) herbal extracts, including bitter candy tuft (*Iberis amara*; 15%), chamomile flower (*Matricariae flos* from *Matricaria chamomilla*; 20%), caraway fruit (*Carvi fructus* from *Carum carvi*; 10%), lemon balm leaf (*Melissae folium* from *Melissa officinalis*; 10%), peppermint leaf (*Menthae piperitae folium* from *Mentha* × *piperita*; 5%), liquorice root (*Liquiritiae radix* from *Glycyrrhiza glabra*; 10%), angelica root (*Angelicae radix* from *Angelica archangelica*; 10%), milk thistle (*Cardui mariae fructus* from *Silybum marianum*; 10%), and greater celandine herb (*Chelidonium majus*; 10%). This preparation has been further refined to STW 5-II (Iberogast ADVANCE), with the omission of the last three of these extracts to focus on the stomach and intestine and modification of the concentrations of some of the other extracts; concentrations were increased to 30% for *Matricariae flos*, 15% for *Melissae folium*, 20% for *Carvi fructus*, and 10% for *Menthae piperitae folium*.

This review focuses on insights into the potential mechanisms that underlie the effects of STW 5-II in the treatment of patients with FD and IBS. We also highlight similarities in modes of action between STW 5-II and STW 5.

2 | Pathophysiological Concepts of Disorders of Gut–Brain Interaction

A comprehensive overview of FD and IBS pathophysiologies is beyond the scope of this review, and we refer readers to excellent recent reviews covering this topic [2–10]. Figure 1 summarizes these pathophysiologies, which include alterations in GI motility [11–13], visceral pain as a result of altered processing along visceral afferents together with signaling along the gut–brain axis [14], altered excitability of enteric neurons [15–17], altered bile acid metabolism [18], impaired gut barrier-protective function [19–21], also referred to as leaky gut, inflammation [22], altered mucosal secretion [23], as well as intolerance of a range of dietary factors [3, 24–26]. Genetic susceptibility and environmental factors, including psychological distress [27], previous GI infection [28] or alterations in the GI microbiome [29], may trigger these pathophysiological changes to evoke symptoms [2, 29].

3 | Mechanisms of Action of STW 5-II

Several clinical studies have demonstrated that STW 5-II and STW 5 improve GI symptoms in FD, comparably with pharmaceutical drugs, including metoclopramide and cisapride (Table 1) [30–39]. Extensive research on the mechanisms that may underlie the efficacy of STW 5-II and its constituent extracts to relieve symptoms in patients with DGBIs has shown effects on GI motility, visceral sensitivity, mucosal barrier function, secretion, and inflammation, as well as the gut microbiome (Figure 2 and Table 2). The effects of individual herbal extracts, as well as some of their interactions, have also been investigated. The following sections review current knowledge about the effects of STW 5-II and STW 5, the extracts they contain, and their interactions on GI motility, visceral sensitivity and nociception, mucosal barrier function, secretion, inflammation, and the gut microbiome.

3.1 | Evaluation of Interaction Effects of Extracts in STW 5-II

To better understand why STW 5-II is effective in DGBIs and how the individual plant extracts may interact with each other, the effects of a number of individual extracts, as well as potential synergistic, additive, or antagonistic interactions of combinations of extracts, have been evaluated. The assessment initially focused on the plant extracts in STW 5 [52, 71], from which STW 5-II has been derived. These plant extracts were studied individually and in combination using human esophageal epithelial cells (Het1A) and intestinal smooth muscle cells (HISMCs) [52]. In these models, the release of IL-8 (a cytokine promoting inflammation in the upper GI tract [72, 73] and also associated with gastroesophageal reflux disease [74]) and Ca^{2+} (as an indicator of motility), under normal and inflammatory (induced using capsaicin or chenodeoxycholic acid (CDCA)) conditions, was quantified after the addition of STW5 or its individual extracts. The release of IL-8 in response to STW 5 was comparable to that in untreated control cells under non-inflammatory conditions, while,

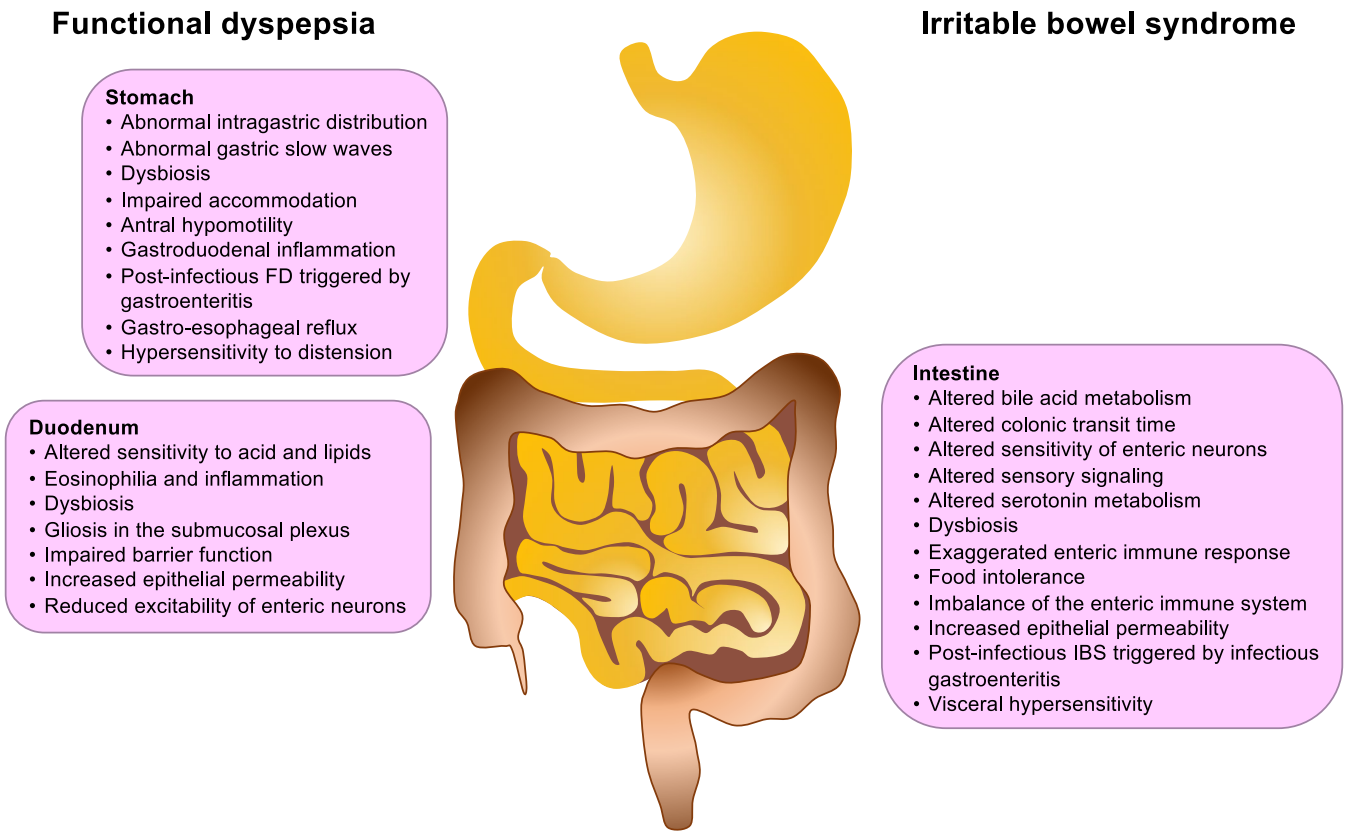

FIGURE 1 | Current concepts of pathophysiological mechanisms underlying functional dyspepsia and irritable bowel syndrome.

under inflammatory conditions, STW 5 treatment reduced IL-8 release to non-inflammatory control levels [52]. Thus, the combination of extracts in STW 5 resulted in an overall anti-inflammatory action, even though the effects of individual extracts varied substantially. To investigate this further, triple combinations of the selected extracts with *Iberis amara* were investigated [52]. The combination index was applied as a measure of potential synergistic effects [75]. The combinations of extracts of *Menthae piperitae folium* and *Matricariae flos* with *Iberis amara* especially showed additive and synergistic effects, respectively. Correspondingly, the lowest inhibitory concentrations (50% of maximum, IC_{50}; 75% of maximum, IC_{75}) were seen for this combination.

In these studies, STW 5 also increased Ca^{2+} release in HISMCs in a concentration-dependent manner. Interestingly, *Melissae folium* as a single plant extract induced the highest Ca^{2+} release, which was further enhanced in combination with *Menthae piperitae folium* and *Matricariae flos*, especially under inflammatory conditions [52]. Since these extracts are also in STW 5-II, the findings suggest that STW 5-II may also induce Ca^{2+} release, although not synergistically; however, this remains to be investigated. These findings should also be seen in the context of studies using intestinal tissue. For example, STW 5-II profoundly relaxes fundus muscle and enhances antral contractility, even though individual components have effects that oppose each other [40], with the strong relaxatory effect most likely due to *Matricariae flos* extract and the prokinetic effect due to *Carvi fructus* and *Melissae folium* [40]. Moreover, prosecretory effects have been reported for three components in STW 5, i.e., *Angelicae radix*, *Menthae piperitae folium*, and *Melissae folium* [49]; however, the prosecretory effects of their combination, or a combination of all extracts, did not differ from those of STW 5, arguing in favor of an additive effect.

3.2 | Targeting Gastrointestinal Motility Disorders

Studies in preclinical models have provided information on the mechanisms of action that may underlie the effects of STW 5-II to relieve symptoms in FD [43]. In isolated guinea pig longitudinal and circular muscle preparations from the fundus, STW 5-II, in concentrations of 64–512 µg/mL, reduced muscle tone in a concentration-dependent manner. These concentrations are lower than those expected from the therapeutic dose (20 drops = 1 mL containing 57.6 mg STW 5-II) in the stomach [43] and, therefore, well within the clinically relevant range. Specifically, the resting human stomach contains about 35 mL of liquid [76], which would result in an STW 5-II concentration of 1.6 mg/mL. That said, it is important to bear in mind that the concentration required for a pharmacological effect may not be the same as the concentration occurring in the lumen of the stomach or intestine. In contrast to findings in the proximal stomach, STW 5-II concentration-dependently increased the amplitude of spontaneous contractions in both the circular and longitudinal muscles of the antrum [43]. These effects were sustained until STW 5-II was removed from the organ bath chambers and were completely reversible by washout. A direct comparison of STW 5-II and STW 5 revealed equipotent effects

TABLE 1 | Effects of STW 5 or STW 5-II in clinical studies.

Indication	Treatment (dose/duration)	Study design	*N* per treatment arm	Endpoint(s)	Inclusion criteria	Results outcome	Refs.
STW 5							
FD	STW 5 or placebo (3 × 20 drops/day for 4 weeks	Phase II, multi-center, placebo-controlled, double-blind, randomized, three-armed	STW 5: 20 Placebo: 20	Efficacy, tolerability	Patients (25–70 year) with persistent or recurrent FD (Rome I criteria) for at least 6 months	The decrease in the GI symptom score was greater in the STW 5 group (from 11.4 to 3.3), than in the placebo group (from 10.4 to 8.9) ($p < 0.001$)	[30]
FD	STW 5 or placebo (3 × 20 drops/day for 8 weeks)	Phase III, multi-center, double-blind, randomized, placebo-controlled	STW 5: 157 Placebo: 151	Efficacy, tolerability, therapeutic safety	Patients (18–80 years) with persistent or recurrent FD (Rome II criteria) for at least 6 months	The GI symptom score was decreased by [mean (SD)] 6.9 (4.8) in the STW 5 group and by 5.9 (4.3) in the placebo group ($p = 0.041$). 17.7% of patients and 20.6% of investigators assessed the efficacy of STW 5 as "very good" compared with 10.8% of each for placebo	[31]
FD	STW 5 or placebo (3 × 20 drops/day for 4 weeks)	Phase II, multi-center study, double-blind, randomized, placebo-controlled	STW 5: 44 Placebo: 42	Efficacy, tolerability, therapeutic safety	Patients (18–85 years) with FD (Rome II criteria)	The GI symptom score decreased from [mean (SD)] 11.6 (4.4) to 5.0 (4.3) in the STW 5 group and from 12.1 (4.7) to 7.5 (6.6) in the placebo group ($p = 0.03$)	[32]
FD	STW 5 (3 × 20 drops/day for 11 days) or metoclopramide (varying doses: 3 × 20–30 drops/day for 10 days)	Retrospective, epidemiological cohort study with parallel groups	STW 5: 490 Metoclopramide: 471	Resolution of symptoms based on GI symptom score at end of treatment	Private practice patients (mean age: STW 5, 38.6 years; metoclopramide, 41.8 years) presenting with persistent or recurrent FD	At the end of treatment, 71.6% of patients on STW 5 were symptom-free, compared with 62.8% on metoclopramide ($p = 0.012$). Tolerability was assessed as "very good" by 90.0% of clinicians for STW 5 and by 70.6% for metoclopramide ($p < 0.001$)	[33]
FGIDs	STW 5 (3 × 20 drops/day for 3 weeks)	Prospective, observational study	272 (80% gastroduodenal origin, 20% intestinal origin)	Time of onset of effect of STW 5, safety	Patients (> 18 years) with FGIDs (Rome III criteria)	Symptom severity decreased by a mean of 1.4 (on 10-unit VAS) 15 min after the first dose. Max. decrease measured was 3.2 (out of 10) and was in 90% achieved at 1 h. The mean (SD) GI symptom score decreased by 9.0 (6.2) after 3 weeks of treatment. Use of descriptive statistics	[34]

(Continues)

TABLE 1 | (Continued)

Indication	Treatment (dose/duration)	Study design	*N* per treatment arm	Endpoint(s)	Inclusion criteria	Results outcome	Refs.
STW 5 II							
FD	STW 5-II or placebo (3×20 drops/day for 12 weeks)	Multi-center, double-blind, placebo-controlled, cross-over RCT	STW 5-II:59/59/86[a] Placebo: \59/59/26	Change of GI symptoms from baseline	Patients (21–70 years) with persistent or recurrent FD (Rome I criteria) for at least 6 months	Greater reduction of GI symptoms after STW 5-II than placebo at 4 (Δ 5.9 vs. Δ 2.6) and 8 (Δ 5.9 vs. Δ 2.6) weeks (both $p < 0.001$). At 12 weeks, treatment assigned based on the response to treatments during the preceding period: adequate symptom control in 95.6% of responders to STW 5-II, and in 78% of non-responders to placebo	[35]
FD	STW 5-II or placebo (3×20 drops/day for 8 weeks)	Multi-center, parallel-group, double-blind, placebo-controlled RCT	STW 5-II: 139 Placebo: 133	Response rate and improvement in GI symptoms relative to baseline	Patients (18–85 years) with FD (Rome II criteria)	STW 5-II increased the response rate (61.2 vs. 45.1%; $p = 0.008$), non-significant improvement of GI symptoms (7.9 ± 4.4 vs. 6.7 ± 4.9 with placebo; $p = 0.07$). Post hoc analysis in Rome IV subgroup revealed a significant response rate (65% vs. 48.7 with placebo; $p = 0.01$). No difference in adverse events between STW 5-II and placebo	[36]
FD	STW 5-II or placebo (3×20 drops/day for up to 8 weeks)	Meta-analysis of RCTs	STW 5-II: 193 (at 4 weeks) 164 (at 8 weeks) Placebo: 190 (at 4 weeks) 162 (at 8 weeks)	Overall and individual symptoms at 4 and 8 weeks, safety	Patients (18–78 years) with FD (Rome IV criteria)	STW 5-II improved overall symptoms, as well as symptoms of fullness, early satiety and epigastric pain, vs. placebo, at 4 and 8 weeks ($p < 0.05$). No difference in adverse events between STW 5-II and placebo	[37]
STW 5 or STW 5 II							
FD	STW 5, STW 5-II (3×20 drops/day for 4 weeks) or cisapride (3×10 mg tablets/day for 4 weeks)	Multi-center, parallel-group, double-blind, double-dummy, active-controlled RCT	STW 5: 61 STW 5-II: 61 Cisapride: 61	Change in GI symptoms relative to baseline	Patients (21–70 years) with dysmotility-like FD	Non-inferiority of STW 5 (change in GI symptoms: Δ 12.1) and STW 5-II (Δ 11.6) vs. cisapride (Δ 10.9; $p < 0.001$)	[38]

(Continues)

TABLE 1 | (Continued)

Indication	Treatment (dose/duration)	Study design	*N* per treatment arm	Endpoint(s)	Inclusion criteria	Results outcome	Refs.
IBS	STW 5, STW 5-II or placebo (3 × 20 drops/day for 4 weeks)	Multi-center, parallel-group, double-blind, placebo−/active-controlled RCT	STW 5: 51 STW 5-II: 52 Placebo: 52	IBS symptom score, abdominal pain score, relative to baseline, safety	Patients (25–60 years) with persistent IBS (abdominal pain or discomfort for at least 3 months in the last 12 months, and constipation, diarrhea or alternating bowel habits)	STW 5 and STW 5-II reduced both the total abdominal pain score (intention-to-treat: STW 5, STW 5-II, both $p < 0.001$) and the IBS symptom score (intention-to-treat: STW 5, STW 5-II, both $p < 0.001$) at 4 weeks modestly compared with placebo	[39]

Abbreviations: FD, functional dyspepsia; FGIDs, functional gastrointestinal disorders; GI, gastrointestinal; IBS, irritable bowel syndrome; RCT, randomized controlled trial; VAS, visual analogue scale.
[a]This study with pre-planned and optional cross-over design consisted of 3 × 4-week treatment periods totaling 12 weeks, plus a 12-week follow-up period. *n* refers to numbers in each 4-week block.

on gastric motility [43], suggesting that the omission of three extracts had no negative influence on efficacy. These region-specific effects in isolated tissue indicate that STW 5-II may restore disordered motility in FD by relaxing the proximal stomach, whereas enhancement of antral contractions could support gastric emptying. The translational significance of these results is underscored by findings that the effect of STW 5 is identical in human gastric muscle strips [40].

Further information on the mechanisms of action stems from studies with STW 5 showing that the effects were nerve-independent [41]. A comprehensive pharmacological study identified store-operated calcium entry channels (SOCE), most likely ORAI channels, and their modulation by protein kinase C and inositol triphosphate receptors, as targets to evoke muscle relaxation [42]. The findings suggested that STW 5 closed SOCE, which caused a decrease in intracellular Ca^{2+} levels and consequently a decrease in muscle tone. Based on the identical effects of STW 5 and STW 5-II on gastric fundus relaxation, it is plausible that both compositions act through the same mechanism(s). It is noteworthy that active components, such as apigenin, luteolin, and (−)-α-bisabolol from *Matricariae flos*, citral from *Melissae folium*, and menthol from *Menthae piperitae folium*, relax smooth muscle in different models by blocking calcium channels or interfering with the release of Ca^{2+} from intracellular stores [77–80]. In addition, licochalcone A, a bioactive chalcone found in *Liquiritiae radix*, can inhibit ORAI1 in T lymphocytes [81]. In addition to the relaxation of the proximal stomach, STW 5 reduces muscle tone in isolated human colon muscle strip preparations [46]. This inhibition of motility was mimicked by extracts of *Menthae piperitae folium*, *Liquiritiae radix*, *Melissae folium*, and *Matricariae flos*. All four extracts are present in STW 5-II, so it seems plausible that STW 5-II also inhibits motility in the large intestine.

A recent study in healthy humans confirmed the effects of STW 5-II observed in preclinical studies [45]. Thus, STW 5-II, when administered acutely in the clinically recommended dose of 20 drops, increased relaxation of the proximal stomach, as measured by an increase in the volume of an intragastric barostat bag, and the motility index of antral pressure waves, compared with placebo, consistent with the preclinical findings. STW 5-II also increased the amplitude, but not the number, of pyloric pressures, but did not affect pyloric tone. These combined motility effects suggest an effect on intragastric distribution. No effects were found on duodenal or esophago-gastric junction pressures. Similar to the preclinical findings, the effects in humans on proximal gastric relaxation and antral pressures did not differ between STW 5 and STW 5-II [44].

3.3 | Targeting Visceral Hypersensitivity and Abdominal Pain

Visceral afferent hypersensitivity plays a key role in DGBIs [82]. STW 5 given to anesthetized rats desensitized small intestinal afferents [62], supporting its role in therapeutic relief in patients with FD. Moreover, intestinal afferent sensitivity to bradykinin, a key mediator of sensitization of spinal afferents and generation of visceral pain, was significantly reduced following STW 5-II application [64]. In a rat model of colitis induced by trinitrobenzene sulfonic acid (TNBS), a combination

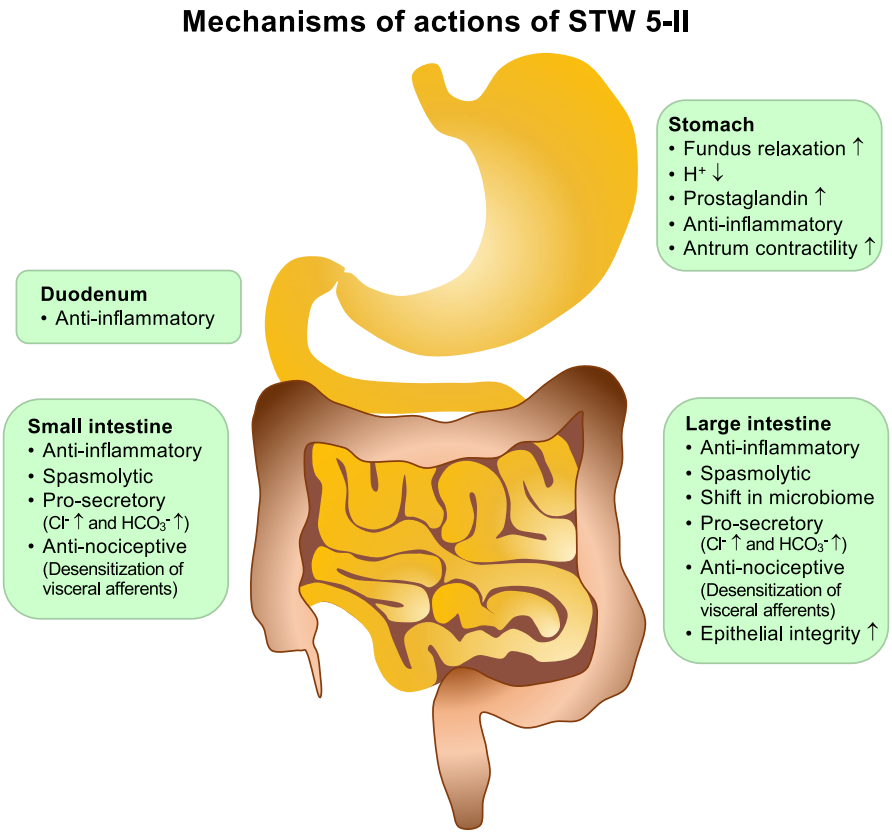

FIGURE 2 | Mechanisms of action of the herbal formulation, STW 5-II, that may underlie its beneficial clinical effects in patients with functional dyspepsia and irritable bowel syndrome.

of peppermint oil and caraway oil had an inhibitory effect on the exaggerated visceromotor response to colorectal distension observed in rats following colitis recovery [83]. Interestingly, neither agent had any inhibitory effect on post-inflammatory visceral hyperalgesia when administered alone, which supports a synergistic or additive action that remains to be fully elucidated. Moreover, whether the effects of these oils reflect those of the extracts in STW 5-II or STW 5 remains to be established. In cultured DRG neurons, activation of these sensory neurons by repeated application of STW 5 showed desensitization involving TRPA1 and TRPV1 receptors [63], potentially representing an anti-nociceptive mechanism induced by STW 5 (and, thus, perhaps also STW 5-II). A recent study showed that STW 5-II impacts nociceptive pathways to relieve abdominal pain through a mechanism involving a reduction in neuronal activation in the spinal cord and corticolimbic regions of the brain [65]. Specifically, in two well-characterized rodent models, STW 5-II attenuated chronic stress-induced and post-inflammatory colonic hypersensitivity. In these experiments, one cohort of adult rats was exposed to repeated water avoidance stress (1 h/day for 10 days), and sham-treated rats served as controls. A second cohort was exposed to intracolonic administration of TNBS to induce a short-lived colitis followed by post-inflammatory visceral hypersensitivity. Rats treated with intracolonic saline served as controls. In both cohorts, colonic sensitivity was quantified as the number of abdominal contractions to graded pressures (0, 20, 40, and 60 mmHg) of isobaric colorectal distension (CRD). As a molecular marker of neuronal activity, extracellular signal-regulated kinase (ERK1/2) phosphorylation was assessed in the brain, spinal cord, and DRGs. Rats exposed to stress or post-colitis showed significantly increased colonic sensitivity compared with controls. Exposure to stress or TNBS also enhanced CRD-evoked ERK1/2 phosphorylation in the spinal cord, DRGs, and brain. Oral administration of STW 5-II decreased colonic sensitivity compared with vehicle control and reduced CRD-evoked brain, spinal, and DRG ERK1/2 phosphorylation. These findings suggest that STW 5-II reverses both stress- and post-inflammatory-induced colonic hypersensitivity by altering neuronal activation in the spinal cord and corticolimbic regions of the brain, which could explain its clinical efficacy in relieving visceral hypersensitivity-related sensory symptoms, including abdominal pain and bloating in DGBIs.

3.4 | Targeting Stress-Mediated Pathophysiological Cascades

It is well recognized that altered signaling along the gut–brain axis contributes to the pathophysiology of FD and IBS [84, 85], and that chronic stress favors IBS development [86] through interference with the CRF/hypothalamic–pituitary–adrenal axis [87]. In an experimental stress-based model of FD, STW 5 exerted its beneficial effects through the gut–brain axis by modulating the activity of CRF [66]. In a model of IBS, rats were subjected to restraint stress, which stimulated the release of serotonin in the colon and the brain, as well as a rise in plasma CRF. The latter was associated with a rise in the colonic mast cell mediators, nerve growth factor, IL-1β, and TNFα. Treatment with STW 5 tended to suppress these changes and normalize intestinal movements [67]. Recent studies on an IBS-like intestinal

TABLE 2 | Effects of STW 5, STW 5-II, or their components in preclinical studies.

Species and models	Methods and readouts	Results	Refs.
Target: Motility			
Guinea pig stomach, human stomach	Motility in muscle strip preparations	STW 5 relaxed circular and longitudinal muscles from proximal stomach, but increased contractility in antral preparations. This effect was mimicked by *Angelicae radix*, *Matricariae flos* and *Liquiritiae radix*; *Chelidonii herba*, *Melissae folium*, *Carvi fructus* and *Iberis amara* evoked contractions. In the antrum, all components, except *Menthae piperitae* and *Cardui mariae fructus*, mimicked the prokinetic effect of STW 5	[40, 41] (Human)
		Relaxation by STW 5 through closure of store-operated Ca^{2+} entry channels (ORAI-type) modulated by protein kinase C and inositol triphosphate receptors	[42]
Guinea pig stomach	Motility in muscle strip preparations	STW 5-II relaxed circular and longitudinal muscle preparations from proximal stomach, but increased contractility in antral preparations. Effect of STW 5-II equipotent to STW 5	[43]
Human (healthy volunteers), stomach, duodenum	Manometry, barostat, radioisotopic gastric emptying measurement	STW 5 increased proximal gastric volume and the motility index of antral pressure waves without affecting pyloric or duodenal pressure. No effect on gastric emptying of solids or intragastric meal distribution	[44]
Human (healthy volunteers), stomach, esophagus, duodenum	High-resolution manometry, barostat	STW 5-II increased proximal gastric volume, stimulated antral motility; no effect on pressure in the esophago-gastric junction, pylorus or duodenum	[45]
Human intestine	Motility in muscle strip preparations	STW 5 inhibited muscle contraction and decreased tone in small and large intestine through interactions with Ca^{2+} channels	[46]
Mouse small intestine	Electrical muscle activity	STW 5 reduced amplitude and frequency of slow waves, which was mimicked by *Angelicae radix*, *Matricariae flos*, *Chelidonii herba* and *Menthae piperitae* (only frequency)	[47]
Target: Secretion			
Human intestine, epithelial cell line T84	Ion secretion in mucosa/submucosa preparations, Ussing chamber	STW 5 increased Cl^- and HCO_3^- secretion through cystic fibrosis transmembrane regulator and Ca2+ dependent Cl^-/HCO_3^- channels	[48]
		Prosecretory action of STW 5 was particularly due to *Angelicae radix*, and partly due to *Menthae piperitae* and *Melissae folium*	[49]
Target: Inflammation			
Rat stomach	Evaluation of gastroprotection after indomethacin-induced gastric ulcer	STW 5, STW 5-II, and all their components reduced acid output, increased mucin secretion, reduced leukotriene production, and increased PGE2. This contributed to the antiulcerogenic effect	[50, 51]
Human epithelial cell line Het1a	Irritant-induced inflammation, interleukin 8 (IL-8) measurements	STW 5 inhibited IL-8 release in chenodeoxycholic acid-challenged epithelial cells	[52]

(Continues)

TABLE 2 | (Continued)

Species and models	Methods and readouts	Results	Refs.
Rat model of esophagitis	Reflux esophagitis after ligation of the pylorus and fore-stomach, esophageal homogenates	STW 5 prevented reflux-induced esophageal lesions and inhibited the increase of inflammation markers (myeloperoxidase, thiobarbituric acid-reactive substances, TNFα, IL-1β)	[53]
Rat stomach and duodenum	Diclofenac-induced gastro-duodenal lesions, gastric and duodenal homogenates	STW 5 inhibited increase in IL-1β and TNFα in stomach and duodenum, normalized gastric IL-10 levels, duodenal heme oxygenase-1 levels and β-cell lymphoma 2 levels in both tissues. STW 5 prevented histological damage	[54]
Mouse intestinal organoids	Inflammation and tight junction disruption induced by cytokinins+bacterial proteins	STW 5-II and its components reduced overexpression of the pro-inflammatory mediators, pNF-κB, pSTAT1, and iNOS, and restored permeability via attenuating the downregulation of the tight junction protein, ZO-1	[55]
Mouse intestinal organoids	CRF-induced inflammation	STW 5-II reduced CRF-induced inflammation and pro-inflammatory cytokine secretion, inhibited the TLR4 system, and restored mucosal barrier by restoring the expression of the tight junction protein, claudin-2	[56]
Human epithelial cell line NCM460	Pro-inflammatory cytokine cocktail consisting of TNFα, IL-1β, IFNγ	STW 5 and STW 5-II were anti-inflammatory by influencing cytokine secretion via reduced activity of the JAK/STAT1 pathway. Both were equipotent	[57]
Zebrafish intestine	Irritant-induced gut inflammation, histology, and cytokine expression	STW 5 abolished macroscopical inflammation, downregulated the expression of the pro-inflammatory cytokine genes, il1β, il6, il8, and tnfα, and upregulated the expression of the anti-inflammatory genes, il10, and wnt3a	[58]
Rat colon	DSS-induced colitis, histology, markers of inflammation, and apoptosis	STW 5 prevented changes in colon length, colon mass index, inflammatory and apoptotic markers, and histological changes induced by DSS	[59]
Rat colon	DSS-induced colitis, histology, and inflammatory markers	STW 5 reduced glutathione levels, TNFα, cytokine-induced neutrophil chemoattractant-3, glutathione peroxidase, superoxide dismutase and myeloperoxidase activity. STW 5 improved histological scores based on inflammatory infiltrates and mucosal architecture	[60]
Rat jejunum	Gamma irradiation-induced intestinal mucositis, histology	Protection of irradiation-induced injury and apoptosis by STW 5. Downregulation of irradiation-induced TNFα, myeloperoxidase, and diamine oxidase	[61]
Target: Visceral sensitivity, stress, nerve activation			
Anesthetized rats, jejunum	Sensory nerve recordings	STW 5 desensitized intestinal sensory nerves to chemical (5-HT, bradykinin) and mechanical stimuli. No effect on resting spike discharge. Anti-nociceptive action of STW 5	[62]

(Continues)

TABLE 2 | (Continued)

Species and models	Methods and readouts	Results	Refs.
Mouse, DRG neurons	Ca^{2+} imaging in cultured murine DRG neurons	STW 5 increased Ca^{2+} levels in DRG neurons. This desensitized after repeated exposure. Nerve activation was stronger in TRPA1-deficient, but lower in TRPV1-deficient, DRG neurons	[63]
Anesthetized rats, colon	Sensory nerve recordings	STW 5-II reduced intestinal afferent sensitivity to bradykinin. This suggests anti-nociceptive action of STW 5-II	[64]
Anesthetized rats, colon	Visceral hypersensitivity after water avoidance stress or trinitro-benzene sulfonic acid-induced late post-inflammatory hypersensitivity	STW 5-II decreased colonic hypersensitivity and reduced colorectal distension-evoked brain, spinal and DRG phosphorylation of extracellular signal-regulated kinase in both hypersensitivity models	[65]
Rat stomach, plasma	Muscle strip recordings, stress hormones in two models–neonatal maternal separation, restraint stress	STW 5 ameliorated stress-induced motility disturbances and prevented the stress-induced changes in ghrelin, CRF and corticosterone levels	[66]
Rat, colon, brain, and blood	Restraint stress model, colonic transit, biochemical and histopathological assessments	STW 5 reduced stress-induced plasma CRF levels, hippocampal and cortical 5-HT increase, and the rise of nerve growth factor, IL-1β, and TNFα in colonic contents. STW 5 prevented stress-induced decrease of colonic 5-HT content and decrease in colonic motility and transit in response. It prevented the rise in oxidative stress biomarkers, restored normal weight gain and preserved tissue structure	[67]
Human intestine	Enteric nerve cell recordings in submucous plexus preparations	STW 5 increased spike discharge in 51% of neurons in the human submucous plexus reflecting the tetrodotoxin-sensitive prosecretory action of *Angelicae radix*	[48]
Target: Microbiota			
Simulated digestion fluids	Simulation of oral, gastric and small intestinal digestion and analysis of metabolic profile changes	Degradation of STW 5 constituents upon in vitro digestion was incomplete; thus, the majority of STW 5 constituents, if not absorbed, may reach the colon to interact with gut microbiota	[68]
Human fecal microbiota	Measurements of microbial fermentation capacity, SCFA production, and microbial composition	STW 5-II increased gas production and SCFA levels and promoted the growth of beneficial bacteria, such as *Bifidobacteriaceae, Lachnospiraceae, Ruminococcaceae, Erysipelotrichaceae, and Eggerthellaceae*	[69]
Human fecal microcosms	Fecal microbial communities and degradation products in IBS and healthy controls	STW 5 did not influence microbiome composition. However, it interacted with intestinal microbiota. Its degradation revealed metabolites with anti-inflammatory, cytoprotective, or spasmolytic activities	[70]
Rat colon	DSS-induced colitis, assessment of biochemical parameters in colonic homogenates, histopathological examination of the colon	STW 5 effectively prevented dysbiosis, changes in colon length, colon mass index, inflammatory and apoptotic markers, and histological changes	[59]

Abbreviations: CRF, corticotropin releasing factor; DRG, dorsal root ganglion; DSS, dextran sodium sulfate; SCFA, short chain fatty acid.

organoid model have shown that, similar to STW 5, STW 5-II effectively reduced CRF-mediated intestinal inflammation and cytokine secretion [56]. Thus, exposure of organoid cultures to CRF stimulated inflammation and inflammatory mediators (IL-1β, IFNɣ, NF-κB, IL-6, and TNFα) as well as CRF receptor expression, as shown by microarray analyses, qRT-PCR, immunofluorescence, and enzyme-linked immunosorbent assays. STW 5-II dose-dependently reversed these effects. Furthermore, STW 5-II suppressed CRF-stimulated claudin 2 overexpression and serotonin release. It also inhibited the Toll-like receptor 4 system, which is a key player in CRF-mediated signaling. Thus, STW 5-II may reverse post-inflammatory visceral hypersensitivity by inhibiting the activity of CRF-reactive neuroimmune cells, reducing local subclinical inflammation and intestinal permeability, and decreasing exposure of visceral afferents to luminal antigens, leading to "desensitization" of peripheral and central nociceptive pathways. This reasoning is in line with the findings of an in vivo study that oral STW 5-II reduced jejunal afferent discharge in response to the inflammatory mediator, bradykinin [64]. In addition to demonstrating the potential of STW 5-II as a therapeutic for post-inflammatory visceral pain, a recent study showed that the formulation may be beneficial in treating visceral pain arising from 'top-down' stress-induced visceral sensitization [65]. Although the exact mechanism remains to be determined, the CRF-modulatory effects of STW 5-II may also be responsible for its analgesic activity in models of stress-induced visceral hypersensitivity. It is, therefore, possible that STW 5-II inhibits stress-induced visceral hypersensitivity through blockade of pathogenic CRF-mediated neuroimmune signaling via mast cells and other immune modulators to promote restoration of the epithelium and prevent, or reverse, sensitization of visceral afferents by luminal antigens. Thus, the multiple anti-inflammatory activities of STW 5-II and its ability to preserve paracellular permeability and tight junction function and integrity are potential explanations for its clinical effects in FD and IBS.

3.5 | Targeting Mucosal Inflammation

The effects of both STW 5 and STW 5-II on mucosal inflammation have been evaluated in several experimental models. For example, each of the individual extracts of STW 5 and STW 5-II and their collective activity have been examined in indomethacin-induced ulcers in rats [50, 51]. Each extract showed substantial activity in suppressing free acidity and acid output. Both combinations and their individual extracts markedly increased mucin secretion and prostaglandin E_2 release and inhibited indomethacin-induced leukotriene secretion. Furthermore, STW 5-II was more effective in preventing all signs of indomethacin-induced histological changes in the stomach. STW 5 proved to be as effective as antacids (Rennie, Talcid, Maaloxan) against gastric ulcers and even more effective in combatting rebound acidity and inhibiting plasma gastrin levels [51]. In an experimental model of reflux esophagitis, STW 5 dose-dependently reduced the histological severity of esophageal lesions and normalized levels of key inflammatory markers [53]. Further studies have shown the beneficial use of STW 5 as adjuvant therapy with NSAIDs to prevent gastro-duodenal lesions and its superiority to proton pump inhibitors, such as pantoprazole [54].

The effect of STW 5-II on inflammation in IBS was investigated in a mouse organoid model derived from murine intestinal stem cells that resembles the in vivo situation [55]. IBS-associated conditions were mimicked by incubation of the organoid cultures with or without a cocktail containing various cytokines (IFNɣ, TNFα, IL-1β, and IL-6) and bacterial components (lipopolysaccharides and flagellin). Typical inflammatory pathways and key regulators in IBS, including the TNF receptor, inducible nitric oxide synthase, and death receptor pathways, as well as STAT1 and NF-κB signaling, were activated by this treatment, as analyzed by mRNA-based microarray hybridization experiments. Treatment with STW 5-II reversed these inflammatory responses, and specific changes in the inflammatory expression profile observed with microarrays were verified using quantitative real-time reverse transcription PCR, western blotting, and immunohistochemistry.

3.6 | Targeting Impaired Barrier Function and Mucosal Secretion

Irritable bowel syndrome pathophysiology is also associated with disruption of paracellular permeability in the intestinal epithelium [19, 20], which is controlled by tight junction proteins. Impaired epithelial integrity has also been found in the duodenum of FD patients [21]. Restitution of cell-to-cell adhesion molecules by STW 5-II may, therefore, contribute to symptom relief in FD. Intestinal organoids treated with the "inflammation cocktail" described above showed reduced expression of ZO-1, and STW 5-II reversed this effect [55]. A functional confirmation of this result was obtained with a fluorescein isothiocyanate permeability assay, showing that STW 5-II does reverse the increased fluorescein isothiocyanate uptake provoked by treatment with cytokines, lipopolysaccharides, or flagellin [55]. As mentioned previously, by suppressing central release of CRF and serotonin, STW 5-II downregulates cytokine-mediated NF-κB activation and, consequently, has a preservative effect on the expression and localization of ZO-1. This effect could explain its ability to reduce intestinal inflammation and IBS-related complications [51, 55–57, 61, 67, 88].

Clinical trials suggest that pharmacological intervention to stimulate epithelial secretion may relieve constipation in patients with chronic constipation or constipation-predominant IBS [23]. STW 5 has strong prosecretory effects in the tissue of the human small and large intestine [48, 49]. Enhanced chloride secretion by STW 5 was due to the activation of cystic fibrosis transmembrane conductance regulator and calcium-dependent chloride channels. Since two of the three extracts responsible for increased chloride secretion (*Melissae folium* and *Menthae piperitae folium*) are present in STW 5-II, it is plausible that it also increases epithelial ion secretion, but this has not been investigated.

3.7 | Targeting the Gut Microbiome

Plant secondary metabolites, such as polyphenols, alkaloids, and terpenoid glycosides, are generally indigestible by host-derived enzymes and/or poorly absorbed and, in this way, can affect the gut microbiota and host in several ways [89]. In addition,

most STW 5-II constituents are stable under simulated upper intestinal conditions in an in vitro digestion model and, if not absorbed, can reach the colon to interact with gut microbiota [68]. Consequently, the enormous metabolic capacity inherent to the gut microbiota can convert these compounds into "new" metabolites that may have better bioavailability and pharmacological activity than their progenitors, explaining the beneficial effects of the product [90, 91]. Furthermore, these compounds may elicit pre- and/or antibiotic effects that influence the gut microbiome and be beneficial via ecological shifts in the gut microbiota [92, 93]. Indeed, some herbal medicines have been shown to positively affect gut symptoms in FD and are presumed to elicit antimicrobial effects towards pathogenic microbes in both animals produced for food and humans [94, 95]. Although an interplay of herbal medicines with the autochthonous microbiota resident in different regions of the GI tract is plausible, the actual mechanisms involved are relatively unstudied. In fact, the impacts on the gut microbiota of many medicinal plants used throughout Europe for GI disorders remain unclear [96].

The impact of STW 5-II on microbial fermentation capacity, short-chain fatty acid production, and microbial composition has been evaluated in a colonic model (SHIME system) adapted for short-term batch experiments using human fecal microbiota from five healthy adult donors [69]. Fecal microbiota metabolization of the constituents of STW 5-II was assessed by UHPLC-HRMS-based metabolite profiling, and the Caco-2/THP1 co-culture assay was used to assess the effect of human fecal microbiota incubates on gut barrier integrity and inflammatory markers. STW 5-II showed prebiotic-like effects with a selective increase in the abundances of probiotic bacterial species, including *Bifidobacteriaceae*, *Lachnospiraceae*, *Ruminococcaceae*, *Erysipelotrichaceae*, and *Eggerthellaceae*, that are thought to confer health benefits. The growth of pathogenic species from the *Enterobacteriaceae* family was suppressed. STW 5-II increased the abundance of Firmicutes, which contain several potential butyrate-producing species, such as *Faecalibacterium prausnitzii*. *F. prausnitzii* has demonstrated gut barrier-protective and anti-inflammatory potency through blocking IL-8 production, inducing the anti-inflammatory cytokine, IL-10, and upregulating regulatory T cells [97, 98]. The increase in *F. prausnitzii* by STW 5-II could add to the anti-inflammatory and tight junction-protective activities observed for STW 5-II [55–57]. *F. prausnitzii* depletion has been observed in IBS patients [98], and an increased abundance of this microbe could play a role in the clinical efficacy of STW 5-II in IBS.

STW 5-II also enriches levels of other butyrate-producing bacteria, such as *Blautia* spp., *Coprococcus comes*, and *Butyricicoccus* spp. Butyrate is a major energy source for colonocytes and has important anti-inflammatory and intestinal barrier-protective functions [99]. Whether this could contribute to the efficacy of STW 5-II in relieving IBS symptoms has not been studied to date. Exposure to STW 5-II also increased levels of acetate- and lactate-producing *Bifidobacteriaceae*, and of propionate-producing *Prevotellaceae* and *Bacteroidaceae*, which are linked to reduced chronic mucosal inflammation in patients with ulcerative colitis [100] and protect the gut mucosa from bacterial invasion [101]. STW 5-II treatment also enriched *Ruminococcaceae* and *Erysipelotrichaceae*, which are depleted in IBS patients [102]. Moreover, lactate production significantly increased in all donors during the first 6 h of incubation, followed by a significant decrease, indicating cross-feeding effects to propionate and butyrate [69]. Branched short-chain fatty acid production, which results from protein fermentation and is associated with detrimental health effects, showed only a minor donor-dependent decrease upon treatment with STW 5-II [69]. In that investigation, enhanced gas production was found in all incubates upon treatment, indicative of increased microbial metabolic activity. However, gas production during STW 5-II fermentation has been reported to be rather mild (~+10 kPa versus control) when compared with results of traditional prebiotics, such as arabinoxylo-oligosaccharides and inulin (+65 kPa) [103].

No effect of STW 5-II has been observed on ammonium production [69]. Experiments in a Caco2/THP1 co-culture model indicated that exposure to STW 5-II protects against inflammation-induced barrier disruption, reduces secretion of the pro-inflammatory cytokine, MCP-1, and increases secretion and stimulates the expression of the anti-inflammatory NF-κB target cytokine, IL-10 [69]. In that study, UHPLC-HRMS analysis identified 110 constituents of STW 5-II that changed levels during incubation with fecal microbiota: 62 constituents that were metabolized, 22 intermittently increased metabolites, and 25 final metabolites, including compounds with established anti-inflammatory activity, such as 18-glycyrrhetinic acid. In another recent study, incubation of STW 5 with human fecal samples from IBS- and non-IBS donors resulted in a rapid metabolic turnover of STW 5 components into specific degradation products, such as 18β-glycyrrhetinic acid, davidigenin, herniarin, and 3-(3-hydroxyphenyl)propanoic acid, which have been described to have anti-inflammatory, cytoprotective, or spasmolytic activities [70].

The effects of STW 5-II on the ecology, growth, and inflammatory tenor of the duodenal mucosa-associated microbiota have also been examined, although this has only been published in abstract form [104]. In this study, the microbial communities in duodenal biopsy tissue from six people with FD and six healthy controls were cultured with a habitat-simulating medium or with the same medium supplemented with variable amounts of STW 5-II (deemed to be equivalent to 0.5×, 1.0×, or 2.0× the recommended single dose). The resulting microbial communities were determined by 16S rRNA gene amplicon profiling. In parallel, the immunomodulatory potential of the "secretomes" produced from the microbial communities was evaluated in vitro, using cultures of a human monocyte-derived cell line designed to quantify NF-κB-modulated gene expression (THP1-luciferase). Although the microbial consortia in the duodenal tissue could be separated via a supervised analysis according to symptom-based criteria (i.e., FD vs. non-FD), STW 5-II, in the doses tested, did not appear to exert major alterations in the microbial communities or in the immunomodulatory potential of their secretomes towards the THP1-luciferase monocyte-derived cultures. As such, the short-term exposure of duodenal microbial communities to STW 5-II did not result in an abrupt and dramatic shift in the gross duodenal microbiota profile, as might be expected with antibiotic use. Instead, its effects might be more subtle, warranting further investigation using approaches with greater resolution or sensitivity than 16S rRNA

gene amplicon sequencing, such as metagenome sequencing and metabolomics.

4 | Open Questions and Remaining Challenges

As outlined in this review, STW 5 and STW 5-II have multiple modes of action. This is, on the one hand, intended and the basis for a multi-targeted approach to treat DGBIs. On the other hand, it remains to be studied why some targets are preferred over others in the various preclinical models, despite being similarly expressed in the various tissues and GI regions evaluated in these models. Future studies need to dissect expression profiles of the various targets in patients to enable more personalized medical treatment. This may also help to reduce the placebo effect in clinical studies, which is as common for STW 5 and STW 5-II as for other drugs used to treat patients with DGBIs.

Because of the complex composition of STW 5-II and STW 5, classical pharmacokinetic and/or pharmacodynamic studies have not been performed. However, some in vitro models have provided insights into the bioavailability of the lead substances. For example, using a static in vitro digestion model, which uses a digestive cocktail representing oral, gastric, and small intestinal digestion processes, it was shown that constituents of STW 5 are partly, but not fully, degraded and, hence, may reach the colon, where they have the capacity to modulate microbiota activity [68]. The everted sac technique was used to evaluate mucosal absorption of lead substances of STW 5 and to measure their appearance in the serosal compartment [105]. There was a substantial and prompt uptake of lead substances, explaining their action(s) on cells in the gastrointestinal wall. Accordingly, this study also provided an indication of the bioavailability of constituents in STW 5-II. However, further studies are required to establish the absorption and bioavailability of STW5 and STW 5-II, as well as their constituents and metabolites, whether they appear in meaningful concentrations in the systemic circulation, and the relationships with their clinical effects in humans. However, this may prove to be challenging due to the very low concentrations involved.

A better understanding of the reasons why, depending on the readouts, antagonistic, additive, synergistic, and sometimes non-additive effects of combinations of individual extracts have been reported, will also be important.

With regards to safety and adverse effects, a recent meta-analysis showed that while STW 5-II improved FD symptoms, severe adverse events did not differ from those of placebo [37], suggesting that if constituents reach the systemic circulation, they do not reach levels relevant for safety concerns. We are not aware of studies revealing drug–drug interactions with STW 5-II, which is consistent with the lack of reports of such cases in clinical studies [37]. In this context, it is important to recognize that while herbs that are contained in STW 5-II may have adverse effects, and warnings or precautions have been issued, the concentrations used are 2.5–90-fold lower than those given in monographs of the herbs (for monographs, see ref [106]).

The different characteristics of patients who benefit from STW 5-II versus non-responders remain not well understood, as is the case for many drugs. Such knowledge, together with the predominant pathophysiology of a given patient group, may assist with targeted treatment by combining particular extracts.

Last, but not least, it is hoped that this review will encourage further multi-center clinical studies, which may address some of the above questions and also how STW 5-II compares to other available drugs.

5 | Conclusion

The currently available treatments for FD and IBS often fail to provide adequate symptom relief in the majority of patients. The phytomedicine, STW 5-II, has been shown in extensive preclinical studies to act on several pathogenic pathways relevant to FD and IBS, including gastrointestinal motility, visceral pain, inflammation, gut barrier function, and the gut microbiota. These effects may, thus, contribute to the ability of STW 5-II to alleviate symptoms in these conditions.

Author Contributions

All authors contributed to the writing of the manuscript and approved the final version.

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Conflicts of Interest

A.A. has been a consultant for Bayer/Steigerwald. R.B. has been a scientific collaborator and consultant for Bayer/Steigerwald. T.E. has been a scientific collaborator and consultant for Bayer/Steigerwald. M.T.K. has been a consultant for and received research funding from Steigerwald and Bayer. M.S. has been a consultant for Bayer/Steigerwald. G.U.-M. has received research support from and has been a consultant for Bayer/Steigerwald. C.F.-B. has received research support from and has been a consultant for Bayer/Steigerwald.

Data Availability Statement

The authors have nothing to report.

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