Mechanism of Action of STW 5 in Functional Dyspepsia and IBS: The Origin of Multi-Target

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Keywords

Multi-target · Gastrointestinal motility · Anti-inflammatory effects · Hyperacidity · Mucosal secretion

Abstract

Background: STW 5 is a complex herbal combination preparation composed of 9 different herbal extracts. As an herbal medicinal product, this preparation is indicated for treating functional dyspepsia (FD) and irritable bowel syndrome (IBS). Its efficacy and practical applicability was demonstrated in several clinical studies. **Summary:** Each herbal constituent of STW 5 has distinct effects on the gastrointestinal tract, and each shows activity through different mechanisms of action: among others, the single extracts have effects on nerves, smooth muscles, epithelial, and inflammatory cells. For example, they have relaxing or tonicizing effects on gastrointestinal muscles, and they counteract inflammation through different physiological systems, contributing to the clinical efficacy through modulation of multiple therapeutic targets. **Key Messages:** STW 5 is a role model for the concept of multi-targeting in therapy. Especially in complex syndromes such as FD and IBS, simultaneous multi-targeting of different functional causes seems to be a more promising approach than the classical paradigm of one disease – one receptor – one effect.

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Published by S. Karger AG, Basel

Introduction

Functional gastrointestinal diseases (FGID) such as functional dyspepsia (FD) and irritable bowel syndrome (IBS) present a therapeutic challenge, as they are characterized by different gastrointestinal symptoms, proposed to originate from several different pathomechanisms. Although the exact etiology of these disorders is still unclear, the factors and mechanisms summarized in Table 1 have all been postulated as underlying causes of these disorders, and most seem to play a role in the development of the heterogenous symptomatology.

The herbal medicinal product STW 5 (Iberogast) is a combination of 9 herbal extract preparations. Its clinical efficacy against FD and IBS has been proven in a number of randomized prospective clinical studies.

Pharmacological examinations using various models suggest that the observed efficacy of STW 5 could be due to different activities of the 9 well-defined herbal extracts at multiple sites. This principle, which is quite popular in clinical medicine, was introduced as multi-target therapy for functional bowel disorders. Components of STW 5 reduce gastrointestinal hypersensitivity and show spasmolytic activities on spastic, but tonicizing on atonic gastrointestinal muscles. In addition, a stimulating effect on reduced mucus secretion, an inhibitory effect on enhanced gastric acid secretion and anti-inflammatory ef-

Table 1. Postulated disorders and mechanisms for the development of functional gastrointestinal complaints including functional dyspepsia and irritable bowel syndrome

Motility disorders	Postprandial antral hypomotility Reduced relaxation of the gastric fundus Decreased or impaired gastric emptying Changes of the gastric electric rhythm Gastro-esophageal reflux Duodeno-gastric reflux
Visceral hypersensitivity	Increased perception of distention Impaired or altered perception of acid Visceral hypersensitivity as a consequence of chronic inflammation
Mucosal inflammation	<i>Helicobacter pylori</i> infection Low grad inflammation Mast cell accumulation and proximity to nerve endings
Changes in acid secretion and duodenal mucosal perception	Hyperacidity Increased perception of acid and fat
Stress	
Psychological disorders and abnormalities	
Genetic predisposition	

fects have been shown. Whether a combination of these effects could be clinically superior remains to be shown, but would offer a logical approach for the use of substances with a multi-target action to treat multi-factorial disorders. These effects could explain the clinical efficacy of STW 5 in a large range of symptoms, and the fact that it improves all FD symptoms and all sub-types of IBS.

Activity of STW 5 (Iberogast)

STW 5 (Iberogast) is a fixed combination of 9 medicinal plant extracts, namely bitter candy tuft (*Iberis amara*) fresh plant extract and extracts of lemon balm leaf (*Melissa officinalis*), chamomile flower (*Matricaria chamomilla*), caraway fruit (*Carum carvi*), peppermint leaf (*Mentha × piperita*), liquorice root (*Glycyrrhiza glabra*), Angelica root (*Angelica archangelica*), milk thistle fruit (*Silybum marianum*), and greater celandine herb (*Chelidonium majus*). STW 5 has been proven in prospective placebo-controlled randomized clinical studies to improve clinical symptoms in patients with FD and IBS.

To elucidate the basic and cellular mechanisms, a series of mechanistic pharmacological studies have been performed in different systems, analyzing different mechanisms of action and showing a variety of different responses. Many of these studies have been performed with

the fixed combination of the 9 extracts (STW 5), as well as with the individual single herbal components, to identify the contribution of the single extracts to each of the individual effects. From these studies, multiple sites of action were identified – targets which may contribute to the clinical effects of STW 5 in functional gastrointestinal disorders.

Gastric Motility

Growing evidence suggests that dysregulation of gastric motility, characterized by impaired gastric relaxation together with antral hypomotility, represents a key mechanism at least in a subset of FD patients. Antral hypomotility may cause delayed gastric emptying, while abnormalities in proximal gastric function lead to impaired fundus/corpus relaxation with consecutive hypersensitivity to distension [1].

STW 5 has been shown in different in vitro and in vivo models to have pronounced effects on gastrointestinal motility. When studied ex vivo in guinea-pig stomach strips, STW 5 elicited differential effects when applied to muscle strips from the fundus/corpus region versus from the antrum region of the stomach [2, 3]. The effect was myogenic by direct action on the muscle [2]. In the fundus region, STW 5 dose-dependently inhibited the muscle activity,

Fig. 1. Contribution of single constituents to the overall activity of STW 5 in different pathomechanisms of (a) functional dyspepsia and (b) irritable bowel syndrome. Relative effect strengths of each extract are presented in the heat-map as color intensity (light yellow for weak effects to dark green for strong effects). The figure was adapted from Abdel-Aziz, et al. [31].

causing a pronounced fundic relaxation. In contrast, when studied in strips originating from the antrum, STW 5 dose-dependently increased phasic contractile activity.

The mechanisms of these differential, region-specific effects of STW 5 were further investigated by Schemann et al. [3, 4]. It could be demonstrated that the inhibitory effect in the fundus is mainly due to a closure of transient receptor potential (TRP)-channels, especially TRPA1 and TRPC, which are predominantly expressed in the fundus/corpus regions of the stomach. By inhibition of these cal-

cium channels, the tonic or spastic activity of the stomach region was decreased. In contrast to the fundus region, the antrum almost lacks these calcium channels. Here STW 5 induced an increase of calcium influx to the antral muscle by stimulation of L-type calcium channels, inducing the observed stimulatory effect.

In additional experiments, these effects were further analyzed to identify the individual plant extracts inducing these effects. A summary of the results is given in Figure 1a.

The differential effect with stimulation of the antral phasic activity and inhibition (relaxation) of the fundus and corpus would be an ideal combination to counteract impaired fundic relaxation and antral hypomotility, which are both known contributors to the development of dyspeptic symptoms.

This action of STW 5 on gastric accommodation was also studied in vivo in healthy human volunteers. Here too, STW 5 elicited a pronounced fundic relaxation and increased antral motor activity [5], which was in clear correspondence to the reported ex vivo effects. More importantly, the effect occurred with the usual clinical dose of STW 5 within 15 min after oral administration. This human in vivo study, therefore, proves that STW 5 in its usual therapeutic form and dose causes motility effects which would counteract proposed mechanisms of the development of symptoms of FD [5].

In addition to its effects in the stomach, STW 5 also elicited a significant dose-dependent effect on the muscle of the lower esophageal sphincter, by increasing the tone and the contractile response of the sphincter muscle – an effect that was shown to be at least partly mediated by stimulation of L-type calcium channels. The increased tone in this muscle could contribute to the patency and the closure of the lower esophageal sphincter, and thus prevent or decrease gastro-esophageal reflux. Even though this is no clear pathomechanism of FD, it would contribute to upper gastrointestinal symptoms such as heartburn and acid regurgitation. In fact, STW 5 was also shown to have a pronounced protective effect in a model of reflux esophagitis (the pylorus ligated rat). In addition to effects on muscle contractility, the observed effects could also have been mediated by other mechanisms, such as acid suppression and direct anti-inflammatory action [6].

Intestinal and Colonic Motility

IBS is associated with the dysregulation of intestinal motility, reflected in altered bowel habits, intestinal spasms, and abdominal pain. Studies showed that patients with IBS, when compared to normal subjects, had an enhanced motor response to different environmental stimuli such as psychological stress, peptide hormones or fatty meals [1]. Motility can be enhanced or decreased, depending on the individual patient and the individual IBS-subtype. Clinical investigations showed that STW 5 is effective in all IBS subtypes.

This can be partly explained by the dual action of STW 5 on intestinal motility.

When studied in the guinea-pig ileum, STW 5 decreased acetylcholine- and histamine-induced contractions, exerting mainly a spasmolytic effect. However, in relaxed ileum strips, STW 5 showed no spasmolytic action; on the contrary, it increased the basal resting tone and contraction of atonic ileal segments [7, 8]. Therefore, the effect of STW 5 was dependent on the pre-stimulation of the muscle. If the muscle was in a contractile or tonic state STW 5 decreased the activity, whereas when the muscle was in the relaxed state STW 5 increased its activity (eukinetic effect).

Both spasmolytic and tonicizing activities, depending on the basal tone of the intestine, could be observed in further in vivo and ex vivo studies, confirming this dual or eukinetic effect. Tonicizing effects, for instance, were reported in inflammation-induced intestinal dysmotility. In an experimental model of DSS-induced colitis, pretreatment of rats with STW 5 for 1 week effectively prevented inflammation-induced decreased colonic motor response to carbachol or KCl [9]. Similar effects were shown in an ex vivo model of colitis, where STW 5 normalized TNBS-induced attenuated small intestinal and colonic reactivity to acetylcholine [10, 11].

Spasmolytic activities of STW 5 were further demonstrated in isolated neostigmine-challenged mouse small intestines [12], and in human small and large intestinal tissue-preparations [4]. In the latter, STW 5 inhibited both muscle tone and motility index.

In the small intestine and the colon, STW 5 was also investigated for its effect on the electrophysiological behavior of the smooth muscle. STW 5 was a potent modulator of slow wave activity in the rat small and large intestines. It dose-dependently inhibited frequency and size of the slow wave activity, which would have pronounced effects on the contractility and intestinal motility [13, 14].

Visceral Hypersensitivity

Visceral hypersensitivity is one likely underlying mechanism of FGID leading to increased perception of physiological stimuli due to altered processing of gastrointestinal neural input [15]. A majority of patients with FD and IBS respond with lower thresholds to distention in comparison to matched healthy volunteers.

There is some evidence that there is upregulation of afferent mechanisms on the peripheral (intestinal), the pre-vertebral, and the spinal levels. This upregulation could be due to chronic irritation or inflammation, or a physiological answer to a challenge, which at some point

can no longer be reversed. Dyspeptic symptoms can also be typical side effects of certain medications such as non-steroidal anti-inflammatory drugs.

The beneficial effects of STW 5 on hypersensitivity were shown in small intestine and colon in vivo (anesthetized rats, small intestine) and ex vivo (isolated mouse colon-mesenteric nerve preparation). STW 5 significantly reduced visceral mesenteric nerve discharge in response to mechanical distention as well as chemical stimulation with serotonin (5-HT) and bradykinin, in both models [16, 17]. The effect corresponds to a reduction of afferent nerve activity, which as a mechanism of action could contribute to the clinical effect of STW 5 in the treatment of gastrointestinal symptoms.

Since 5-HT is one of the main transmitters in the GI-tract, binding affinities of STW 5 and its constituents were determined for 5-HT₃ and 5-HT₄-receptors, the main serotonin-receptors in the gut. STW 5 interacted mainly with 5-HT₃-receptors [18]. This was further confirmed by measuring its 5-HT₃ receptor-blocking activity in a functional ex vivo test of 5-HT₃-receptor mediated ileal contractions [19]. 5-HT₃ receptors are also known to play an important role in nausea and vomiting, which may contribute to STW 5's clinical benefits in FD.

Inflammation

There is increasing evidence that FD and IBS could be linked to low-level inflammation, causing the respective changes in motility and visceral sensitivity. Especially visceral hypersensitivity could be induced by local inflammation and by changes of mast cell density and their proximity to visceral nerve endings. Inflammatory cells and mast cells have been reported and linked to clinical severity and symptoms of IBS. Whether this effect is induced by bacteria such as *Helicobacter pylori* or other candidates of the altered microbiome, or whether it is due to special food components or drugs remains to be answered.

STW 5 has been studied in several general and in gut-specific models for its effect on inflammation and inflammatory pain responses. Potent anti-inflammatory effects have been shown throughout the GI-tract, both, in vitro and in vivo. Starting at the esophagus, where STW 5 largely attenuated reflux-esophagitis in acute and sub-chronic settings [6, 20]. In the stomach, STW 5 prevented indomethacin-induced inflammation as confirmed by the reduction of leukotriene concentrations, ulcer indices, and prevention of histologically assessed tissue damage [21, 22].

As for the lower GI-tract, several pharmacological models were used to investigate the effects of STW 5 on small intestinal and colonic inflammation. For instance, when tested in an ex vivo model of TNBS-induced intestinal inflammation in ileum and jejunum segments of the rat, STW 5 prevented the TNBS-induced inhibition of ACh-induced contractions. This effect was mirrored in reduced morphological changes induced by TNBS in mucosal and muscle layers [23, 24]. These potent anti-inflammatory effects were also shown in in vivo models of TNBS- and DSS-induced colitis in rats [9, 25]. In yet another in vivo model, STW 5 partially reduced the severity of 5-fluorouracil-induced mucositis in rats on a morphological and functional level [26]. There was even a protective effect against gamma irradiation-induced intestinal morphological and functional changes. Again, the effect was attributed to the inhibition of inflammatory mechanisms [27, 28].

The different in vitro, ex vivo, and in vivo models showed that the potent anti-inflammatory effects of STW 5 are mediated by multiple mechanisms, including the activation of adenosine A_{2A}-receptors, the inhibition of proinflammatory mediators like tumor necrosis factor- α , interleukin-8, and leukotrienes and the enhancement of anti-inflammatory mediators like interleukin-10. However, STW 5's anti-inflammatory effects do not seem to be mediated by COX-inhibition, an effect that contributes to its mucosa-protective activity [12, 23, 29, 30]. While all single extracts contributed to the overall anti-inflammatory effects of STW 5, the strongest actions were seen with bitter candytuft followed by Melissa (Fig. 1) [31].

Furthermore, STW 5 and the 9 individual plant extracts forming the combination were shown to possess potent radical scavenging and antioxidant activities, which could contribute to STW 5's anti-inflammatory and mucosa-protective actions. Pure chemical as well as complex cellular assay systems were used to investigate their effects on different types of reactive oxidative products. All single extracts contributed to the overall effects of STW 5. In chemical systems, single extract effects were additive, in cellular systems, however, a supra-additive effect was detected [32].

Acid Secretion

Another proposed pathomechanism of gastrointestinal symptoms is response to luminal acid, both in the distal esophagus and in the duodenum.

Under certain conditions, STW 5 has the ability to modulate and reduce gastric acid secretion. In an in vivo

setting in rats, STW 5 reduced indomethacin-induced acid hyper-production and prevented the development of mucosal lesions in the stomach. The effect size was comparable to that of commercially available antacids. However, unlike the tested antacids, STW 5 did not cause rebound gastric acid secretion after the effect wore off. The underlying mechanism of action could be a reduction of serum gastrin levels [21, 22]. This effect is expected to be helpful in clinical situations with acid hypersecretion or acid rebound overshoot secretion. The contribution of the different mechanisms (anti-inflammatory action, acid or gastrin suppression, mucosal protection) to the overall activity was not fully elucidated, but all these effects should contribute to the clinical efficacy.

A similar effect was observed when STW 5 was studied in pylorus-ligated rats. Pretreatment with STW 5 dose-dependently reduced acid-induced changes in the esophagus of the rats and normalized the deranged levels of inflammation markers. The effect of the higher dose of STW 5 was similar to the effects induced by proton pump inhibitors [6, 20].

Mucosal Secretion

The effect of STW 5 on mucosal function and intestinal mucosal secretions was studied in Ussing chamber experiments in human intestinal tissue, in a human epithelial cell line (T84) and by recording of the activity of human enteric neurons using a voltage-sensitive dye. STW 5 induced a dose-dependent increase of ion secretion. It also had a secretagogue effect in human intestinal tissue through direct epithelial action and through activation of enteric neurons. The neural prosecretory effect could be attributed to the extracts of angelica, peppermint, and lemon balm. The secretory stimulation effect involved activation of epithelial cAMP- and increased epithelial Cl^- flux via CFTR and Ca^{2+} -activated chloride channels [33, 34]. Overall, the constituents of STW 5 increase secretion of human intestinal epithelium, which could contribute to its beneficial effect in IBS patients.

Conclusions

STW 5 has a proven clinical effect in gastrointestinal disorders, such as FD and IBS. The 9 herbal components of STW 5 exert multiple and differential effects under experimental conditions in vitro and in vivo, influencing various aspects of gastrointestinal function. STW 5 has dif-

ferential effects on gastrointestinal motility, depending on the location and the functional state of the muscle. It potentially relaxes the fundus/corpus region and increases motility in the antrum. It has a tonus-increasing effect on the lower esophageal sphincter, but acts spasmolytic or tonifying in the small intestine and colon, depending on the basal state of the muscle. In addition, STW 5 reduces afferent neural activity triggered by mechanical and chemical stimuli. It has potent anti-inflammatory effects throughout the GI-tract mediated through multiple mechanisms. It reduces the oxidative stress and protects against irritant-induced inflammation, such as TNBS-induced colitis or radiation-induced changes. In line with this finding, STW 5 has been shown to protect against reflux-induced changes in the esophagus and against nonsteroidal anti-inflammatory drugs-induced alterations in the stomach. Finally, STW 5 has stimulatory and protective effects on mucosal integrity and mucosal secretion. It stimulates intestinal and colonic secretion by neural and direct activation of chloride secretion. In total, STW 5 has multiple effects and acts on different structures (direct muscle action, direct action on enteric neurons, direct action on epithelial cells, action on immune cells, and afferent nerves). The single effects are exerted by different components of STW 5 as shown in Figure 1. All effects could contribute to the beneficial clinical effects on FGID shown in randomized controlled clinical studies. The experimental data support the postulated multi-target action of STW 5.

Disclosure Statement

H.A.-A. is fully employed by Steigerwald Arzneimittelwerk GmbH.

H.-D.A. has been active as speaker or advisor for Steigerwald, Germany, Bayer, Germany and Falk Foundation Germany.

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