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Spasmolytic and tonic effect of Iberogast® (STW 5) in intestinal smooth muscle

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Abstract

STW 5 (Iberogast®) is a fixed combination of nine medicinal plant extracts effective in the treatment of functional dyspepsia and irritable bowel syndrome. The effects of STW 5, a combination of *Iberis amara* fresh plant extract, and other eight plant extracts as well as single extract components including extracts from *Menthae piperitae folium*, *Matricariae flos* and *Liquiritiae radix*, were assayed in guinea pig ileum with or without stimulation with acetylcholine or histamine, in order to find a possible effect on the contractility of intestinal smooth muscle.

STW 5 decreased acetylcholine- and histamine-induced contraction of guinea pig ileum. This was also true for extracts of *Menthae piperitae folium*, *Matricariae flos* and *L. radix*. Extract from *I. amara*, however, showed no spasmolytic action; in contrary, it increased the basal resting tone and contraction of atonic ileal segments. This was also true when STW 5 was employed.

A spasmolytic action of STW 5 could also be observed in duodenum, jejunum and colon.

These data are the first to show not only the spasmolytic effects of STW 5 and its component extracts in intestinal muscle but also the tonicising effects of STW 5 through its component *Iberis amara* extract in relaxed intestinal muscle. Thus, pharmacological evidence suggests a dual-action principle and may explain, at least in part, the clinically observed therapeutic efficacy of STW 5 (Iberogast®) in both hypotonic and spastic dysmotility symptoms of functional dyspepsia and irritable bowel syndrome.

Keywords: Functional dyspepsia, FD; Irritable bowel syndrome, IBS; Dysmotility; Duodenum, Jejunum, Ileum, Colon; In vitro; Phytomedicine, STW 5, Iberogast; *Iberis amara*, STW 6; *Mentha piperita*, *Matricaria recutita*, *Glycyrrhiza glabra*; STW 7; Dual-action principle

Introduction

STW 5 (Iberogast®) is a fixed combination of herbal extracts used in the therapy of motility-related diseases of the gastrointestinal tract (Allescher, 2006; Rösch et al., 2006). Its components are an aqueous-ethanolic fresh plant extract from *Iberis amara* totalis and drug extracts from peppermint leaves (*Menthae piperitae folium*), chamomile flower (*Matricariae flos*), liquorice root (*Liquiritiae radix*), angelica root (*Angelicae radix*), caraway fruit (*Carvi fructus*), milk thistle fruit (*Silybi mariani fructus*), lemon balm leaves (*Melissae folium*), and greater celandine herb (*Chelidonii herba*).

Earlier data show spasmolytic properties for Angelica roots on the smooth muscles of the intestinal tract (Izzo

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[1]The data in current publication are derived from experiments conducted between 1985 and 1993. Part of them was preliminary published in 1993 (Okpanyi et al., 1993).

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et al., 1996; Reiter and Brandt, 1985).The same has been found for chamomile flowers extract and its constituents (Achterrath-Tuckermann et al., 1980). Caraway fruits exhibited a concentration-dependent spasmolytic effect both with acetylcholine and with histamine-induced spasm of the guinea pig ileum, as well (Forster et al., 1980). Also for milk thistle fruits, a spasmolytic effect in isolated guinea pig ileum has been demonstrated (Liersch et al., 2003). Lemon balm leaves exerted spasmolytic effects on the ileum of the guinea pig and the duodenum of the rat (Reiter and Brandt, 1985; Forster et al., 1980). A spasmolytic action of peppermint leaves extract is also known (Forster et al., 1980; Forster, 1983). Moreover, for celandine herbs a spasmolytic effect in small intestine has been shown (Sato, 1935; Wrociński, 1960; Weiß, 1991), as well as for liquorice roots (Wrociński, 1960; Chandler, 1985).

In order to confirm part of these data for the extract combination STW 5, studies were conducted with isolated ileum of the guinea pig as well as with isolated duodenum, jejunum, ileum and colon of the rat. Moreover, some components of STW 5 including extracts of *I. amara*, *Menthae piperitae folium*, *Matricariae flos* and *L. radix* were tested using the isolated guinea pig ileum. They not only confirmed the spasmolytic effects in contracted intestinal muscle, but in addition STW 5 and *I. amara* showed tonicising effects in relaxed or only slightly contracted intestinal muscle.

Materials and methods

STW 5 (Iberogast®) contains *I. amara* totalis as a fresh plant extract and eight dried plants as drug extract (Table 1). STW 7 corresponds to STW 5, but without the extract of *I. amara*.

Negative control was a 31.5% v/v ethanol solution as contained in STW 5 and in the single plant extracts; positive control was papaverine.

Table 1. Composition of STW 5 (Iberogast®)

STW 5 contains extracts of	Drug–extract ratio	ml/100 ml
Iberis amara totalis	(1:1.5–2.5)	15
Menthae piperitae folium	(1:2.5–3.5)	5
Matricariae flos	(1:2.0–4.0)	20
Liquiritiae radix	(1:2.5–3.5)	10
Angelicae radix	(1:2.5–3.5)	10
Carvi fructus	(1:2.5–3.5)	10
Silybi mariani fructus	(1:2.5–3.5)	10
Melissae folium	(1:2.5–3.5)	10
Chelidonii herba	(1:2.5–3.5)	10

Extracts contain ethanol 31% (v/v).

The spasmodic agent for the induction of intestinal contraction was acetylcholine at 8–12 concentrations between 0.625 µg and 163 mg/l. In one experiment, histamine at 10 concentrations between 3 µg and 100 mg/l was used. Krebs–Henseleit buffer, aerated with carbogen (95% O_2 + 5% CO_2), kept at a temperature of 37 °C in a water bath, was used as the incubation medium.

For most experiments, guinea pigs of either sex, weighing 250–400 g were used. They were housed at a room temperature of 24 °C and received standard diet (guinea pig diet, Altromin, Lage/Lippe Germany) and tap water ad libitum. In one experiment, male Sprague Dawley rats weighing 700–800 g were used, which were kept at 23 ± 1 °C and received rat standard diet (Altromin). The animals, fasted over-night, were killed by cervical dislocation and bled from the carotid arteries. Five – six animals were tested for each experimental group. Intestinal segments of about 20 mm length were prepared from the terminal ileum of the guinea pig or from the different intestinal sections of the rat. They were cleaned and suspended in a 10 ml organ bath containing Krebs–Henseleit solution, aerated with carbogen. Prior to the measurements, the intestinal segments were allowed to equilibrate for 20 min under a resting tension of 1.0 g. The longitudinal contraction was measured according to the method of Magnus (1904), modified, using an isotonic contraction transducer and amplifier, and recorded with a pen recorder (Okpanyi et al., 1993).

Increasing concentrations of acetylcholine or histamine (agonists) were added to the organ bath non-cumulatively for a full concentration response curve. Then second concentration response curves were obtained, in the presence of the test substances (antagonists) in the organ bath. In one experiment, STW 5, the extract of *I. amara* and the solvent control (31.5% ethanol) were added to the reservoir of the organ bath solution. In the other experiments, the test solutions or the positive control (papaverine in ethanol 31.5%) were added directly to the organ bath 1 min before the addition of the spasmogens (agonists).

Additionally, the effects of STW 5 and of the extracts of *I. amara* and *Matricariae flos* on non-stimulated and non-contracted ileum segments were tested for measuring their influence on the basal resting tone and the spontaneous contractility of the gut.

The effects of the test substances are expressed as percentage of the maximum possible contraction achieved with the spasmogen or as the difference Δ between the EC_{50} of the spasmogen without and with the test substance. The results are expressed as mean ± SEM. The statistical comparison of the respective results with the control and the test substances were conducted with the Student's *t*-test for matched pairs.

Results

Antispasmodic actions

Using the isolated guinea pig ileum as a model, the effects of STW 5 (Iberogast®), STW 7 (STW 5 without extract of *I. amara*) and extracts from *I. amara*, *Menthae piperitae folium*, *Matricariae flos* and *L. radix* on acetylcholine-induced contractions were studied. The extract solvent ethanol served as control and papaverine for comparison. As shown in Fig. 1 and Table 2, STW 5 and STW 7 produced a significant and concentration-dependent inhibition of acetylcholine-induced contraction in the range between 2.5 and 10 ml/l. This was comparable to the effect of 10 and 20 mg/l papaverine. Extracts from *I. amara* showed no inhibitory action.

In a second series of experiments, the antispasmodic effects of some components of STW 5 were tested, which are thought to contribute to its spasmolytic effect on acetylcholine-induced contraction of isolated guinea pig ileum. As shown in Fig. 2, extracts from *Menthae piperitae folium*, *Matricariae flos* and *L. radix* produced a significant inhibition of acetylcholine-induced contraction which is quantified by the data shown in Table 3. Again extracts from *I. amara* were without inhibitory effect. The same was true when the solvent ethanol was employed as a control. Application of the test substance with the organ bath solution (Table 2) or separately 1 min before addition of the spasmogen (Table 3) did not influence the results.

The action of STW 5 was also tested in various segments of the gastrointestinal tract of rats, including duodenum, jejunum, ileum and colon. As is evident from Table 4, in all segments of the gut STW 5 significantly increased the EC_{50} for acetylcholine.

In order to test whether or not the antagonistic effect of STW 5 is limited to acetylcholine-induced contractions, its effects on histamine-mediated contraction was also tested using again the isolated guinea pig ileum. As shown in Fig. 3 and Table 5, STW 5 in concentration-dependent manner significantly inhibited histamine-induced contraction of the guinea pig ileum.

Tonic actions

Whereas, as shown so far, STW 5, STW 7 and the extracts from *Menthae piperitae folium*, *Matricariae flos* and *L. radix* produced inhibition of acetylcholine/histamine-induced contractions of the isolated guinea pig ileum, no such effect could be observed with the extract of *I. amara*. In contrary, it appeared that this extract even showed a tendency to be agonistic to acetylcholine (Figs. 1, 2 and Tables 2, 3). It was therefore of interest to test the effects of STW 5 and the extract of *I. amara* on contractility of isolated guinea

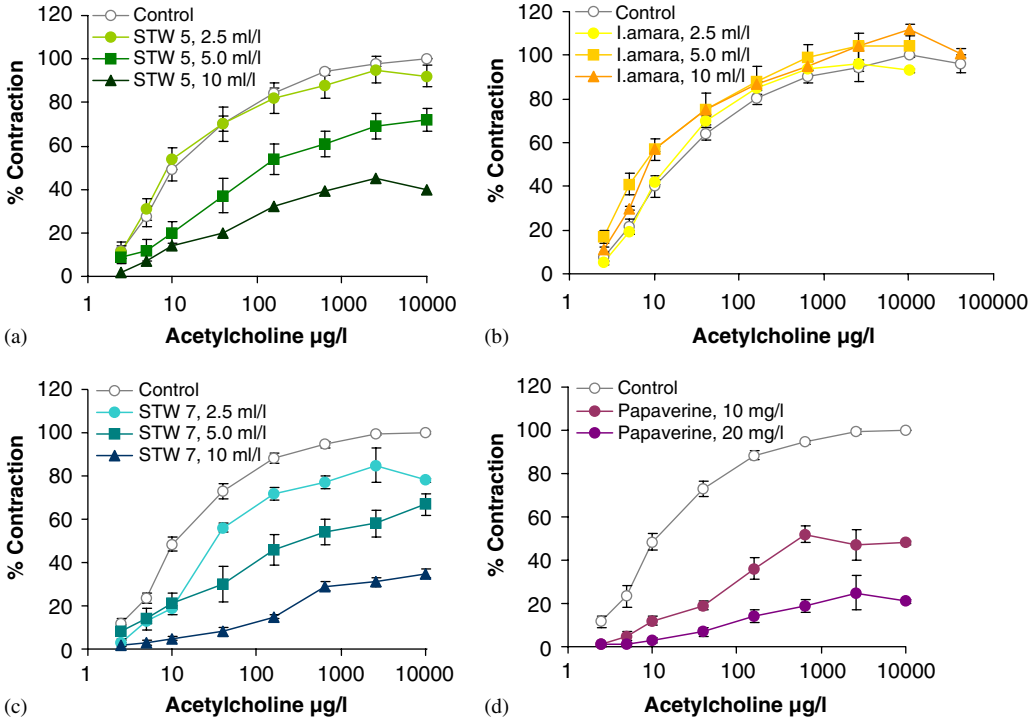

Fig. 1. Effect of (a) STW 5 (Iberogast®), (b) extract from *Iberis amara*, (c) STW 7 and (d) papaverine on acetylcholine-induced contraction of isolated guinea pig ileum (100%, values are mean ± SEM, $n = 5$–6).

Table 2. Effect of STW 5 (Iberogast®), STW 7, extract of *Iberis amara* and papaverine on acetylcholine-induced contraction of isolated guinea pig ileum

Test substance	Concentration of test substance (ml/l)	*N*	Acetylcholine (control) EC_{50} (μg/l)	Acetylcholine + test substance, EC_{50} (μg/l)	ΔEC_{50} (μg/l)
STW 5	1.25	6	14.3 ± 5.1	16.2 ± 6.0	1.9
	2.5	6	19.0 ± 2.2	22.2 ± 3.1	3.2
	5.0	6	14.0 ± 3.7	76.8 ± 24.9	62.8*
	10.0	6	23.2 ± 4.5	57.7 ± 21.3	34.5
STW 7	1.25	6	14.5 ± 4.2	15.3 ± 5.3	0.8*
	2.5	5	21.2 ± 4.4	27.0 ± 8.5	5.8
	5.0	6	11.7 ± 4.1	68.2 ± 25.5	56.5**
	10.0	6	9.3 ± 1.5	178.0 ± 45.0	168.7**
Iberis amara	1.25	6	16.8 ± 3.4	16.8 ± 5.7	0.0
	2.5	6	21.3 ± 3.4	19. ± 3.6	−1.5
	5.0	6	16.8 ± 2.9	9.3 ± 1.0	−7.5*
	10.0	6	31.7 ± 10.8	14.8 ± 4.4	−16.8*
Papaverine (mg/l)	10.0	6	12.7 ± 1.6	88.8 ± 19.6	76.3*
	20.0	5	14.4 ± 3.3	167.2 ± 49.9	152.8*

EC_{50} and SEM are given as acetylcholine concentration in μg/l without and in the presence of test substances. Data were calculated from curves of Fig. 1. *$p \leqslant 0.05$; **$p \leqslant 0.01$.

pig ileum (basal and spontaneous) in the absence of acetylcholine. The contractions in response to STW 5 and *I. amara* extract were calculated as percentage of a standard contraction produced by 2.56 mg/l acetylcholine (data not shown).

As depicted in Fig. 4, *I. amara* extract in concentrations between 0.5 and 1.0 mg/l enhanced spontaneous contraction and basal tone of guinea pig ileum to about 30–50% of the effect of 2.56 mg/ml of acetylcholine. For the extract of *Matricariae flos*, a similar, but much weaker tonic effect was seen (data not shown). For STW 5, an effect similar to that of *I. amara* was observed. However, in this case much higher concentrations of STW 5 were necessary to achieve the same effect as observed with the extract of *I. amara*.

Discussion and conclusion

A spasmolytic effect in intestinal smooth muscle in vitro has been observed in several herbal drugs used in the therapy of motility-related functional gastro-intestinal diseases, the indication in which STW 5 is used. As STW 5 is a combination of several herbal extracts, it seems reasonable to discuss the effects of its components initially, and later those of the combination.

As shown in Fig. 1, Table 2, STW 5 and STW 7 decreased the spasmodic effect of acetylcholine in a concentration-related manner. It appears that STW 7 (STW 5 without *I. amara* extract) at least at 10 ml/l was slightly superior to STW 5. Since *I. amara* extract did not contribute to the spasmolytic action of STW 5 but, as shown in Fig. 4, in contrary exhibited even an increased spontaneous contraction and basal tone in STW 5, this could be a possible explanation for the slight difference in action.

Using papaverine as a positive control, the effects of 10 and 20 mg/l were close to the range of 5 and 10 ml/l STW 7 whereas STW 5 showed slightly less action in comparison to papaverine. Ethanol itself did not affect contractility of isolated guinea pig ileum.

When in a second series of experiments the effects of three plant extracts which are known to possess spasmolytic activities, i.e. *Menthae piperitae folium*, *Matricariae flos* and *L. radix* (Forster et al., 1980; Achterrath-Tuckermann et al., 1980; Wrociński, 1960) were tested, the extract from *Menthae piperitae folium* at equal concentrations exhibited by far the most pronounced action. Here, the effects of *Matricariae flos* and *L. radix* were small in comparison. Moreover, again the extract of *I. amara* did not contribute to the spasmolytic action of STW 5. Thus, since STW 5 is a combination of more or less active components under the conditions of this study, the overall action of STW 5 is less than the effect of *Menthae piperitae folium*. This is not surprising because in STW 5 the extract of *Menthae piperitae folium* accounts only for half of the amounts of extracts, e.g. from *Matricariae flos* and *L. radix*.

The antispasmodic effect of STW 5 is not restricted to the ileum. It also has the duodenum, jejunum and colon as targets. As may be suggested from Table 4, there seems to be different sensitivity in the order duodenum > colon > jejunum > ileum. Whether or not this is relevant for humans remains to be elucidated.

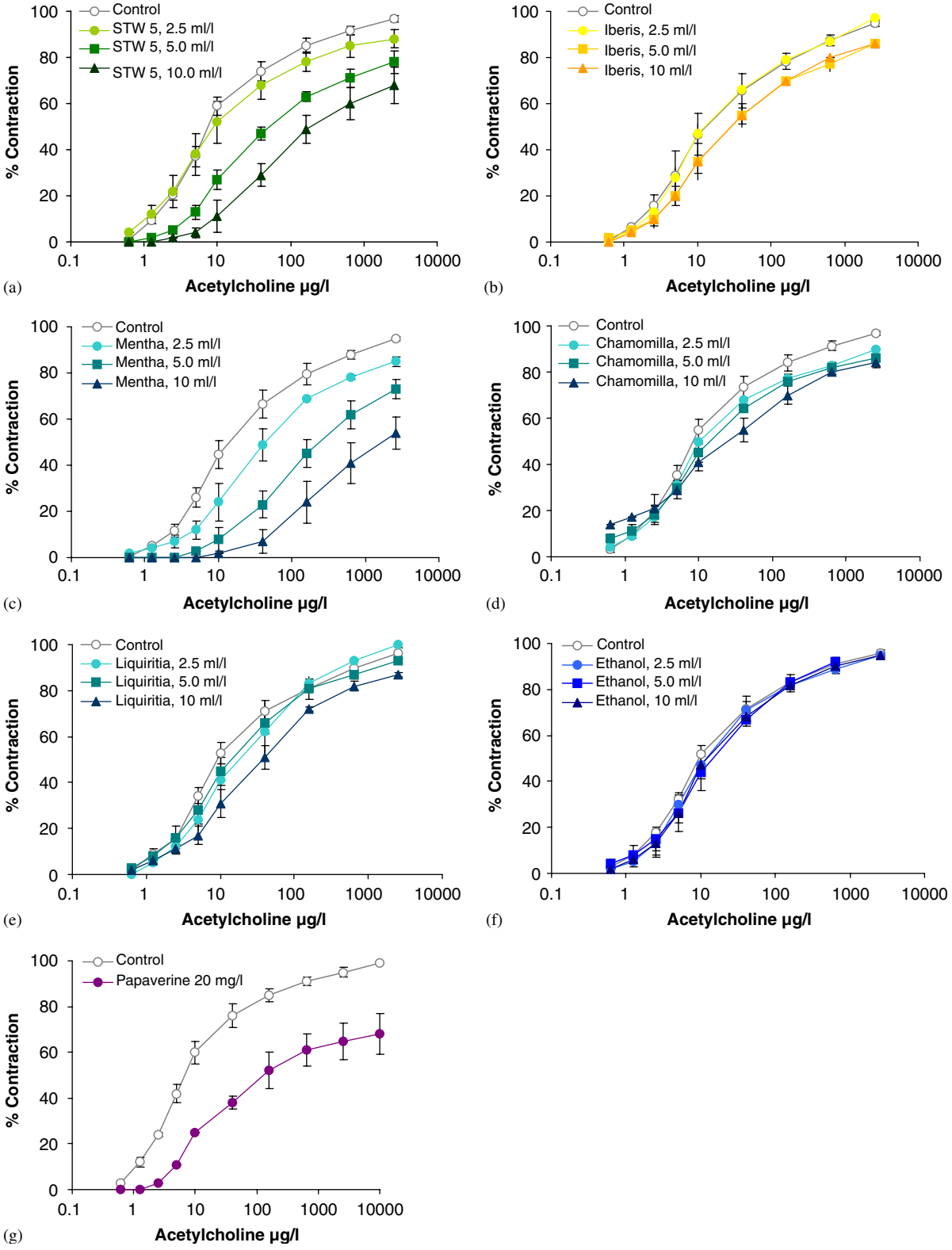

Fig. 2. Effect of (a) STW 5 (Iberogast®), (b) *Iberis amara* extract, (c) *Menthae piperitae folium* extract, (d) *Matricariae flos* extract, (e) *Liquiritiae radix* extract, (f) ethanol and (g) papaverine on acetylcholine-induced contraction of isolated guinea pig ileum (100%, values are means ± SEM, $n = 6$).

Table 3. Effect of STW 5 (Iberogast®), *Iberis amara* extract, *Menthae piperitae folium* extract, *Matricariae flos* extract, *Liquiritiae radix* extract and ethanol on acetylcholine-induced contraction of isolated guinea pig ileum

Test substance	Concentration of test substance (ml/l)	Acetylcholine (control) EC_{50} (μg/l)	Acetylcholine + test substance, EC_{50} (μg/l)	Δ EC_{50} (μg/l
STW 5	1.25	12.4 ± 4.1	13.8 ± 3.1	1.4
	2.5	8.8 ± 2.7	17.2 ± 9.1	8.4
	5	15.2 ± 2.0	34.2 ± 3.9	19.0**
	10	12.0 ± 3.2	104.9 ± 26.8	92.9**
Iberis amara	1.25	25.1 ± 7.2	22.0 ± 5.3	−3.1
	2.5	16.6 ± 4.6	23.2 ± 4.2	6.6
	5	44.5 ± 21.4	33.0 ± 7.1	−11.5
	10	20.8 ± 8.2	27.4 ± 6.2	6.5
Menthae piperitae folium	1.25	9.1 ± 1.0	20.9 ± 5.0	11.8*
	2.5	20.5 ± 6.0	84.1 ± 52.9	63.6
	5	22.0 ± 2.6	281.6 ± 95.5	259.6*
	10	29.4 ± 13.2	1431.2 ± 552.1	1401.8**
Matricariae flos	1.25	16.3 ± 2.5	22.8 ± 9.1	6.5
	2.5	19.1 ± 3.9	19.2 ± 8.2	0.1
	5	13.5 ± 4.3	20.6 ± 8.8	7.1
	10	10.5 ± 3.2	20.8 ± 5.7	10.3**
Liquiritiae radix	1.25	17.6 ± 3.0	19.2 ± 3.3	1.6
	2.5	14.1 ± 4.0	16.3 ± 3.4	2.2
	5	10.5 ± 3.6	17.7 ± 3.7	7.2*
	10	17.5 ± 4.5	32.5 ± 9.4	15.0*
EtOH	1.25	17.9 ± 4.2	19.2 ± 6.4	1.3
	2.5	18.8 ± 3.9	19.6 ± 3.8	0.8
	5	14.3 ± 3.3	22.6 ± 6.0	8.3
	10	12.7 ± 1.4	18.9 ± 3.8	6.2

EC_{50} and SEM are given as acetylcholine concentration in μg/l without and in the presence of test substances. Data were calculated from curves of Fig. 2. $n = 6$. *$p \leqslant 0.05$; **$p \leqslant 0.01$.

Table 4. Effect of STW 5 (Iberogast®) on acetylcholine-induced contractions of isolated rat duodenum, jejunum, ileum and colon

Intestinal section tested	Acetylcholine (control) EC_{50} (mg/l)	Acetylcholine + test substance, EC_{50} (mg/l)	ΔEC_{50} (mg/l)
Duodenum	2.60	6.00	3.40[a]
Jejunum	0.63	1.79	1.16[a]
Ileum	1.08	1.80	0.72[a]
Colon	1.08	2.75	1.67[a]

The EC_{50} are given as acetylcholine concentrations in mg/l without and in the presence of test substances. Data were calculated from respective concentration/action curves of acetylcholine (data not shown). $n = 5$.

[a]Significant difference between test substance and control.

The antispasmodic action of STW 5 is not restricted to the antagonistic action to acetylcholine but is also effective when histamine is used as a spasmodic agent. This indicates that the combined antagonistic action of the plant extracts used for STW 5 is not specific for one or the other. Acetylcholine-induced action relates to muscarinic receptors and histamine to histamine 1 receptors. It is not known whether or not compounds of STW 5 interact with one of these receptors. It is also possible that their actions are not specific for receptors, which is for instance known for the reference compound papaverine. This compound is thought to act via inhibition of cyclic nucleotide phosphodiesterase thus increasing cAMP, which relaxes increased contractility of smooth muscles.

In contrast to the spasmolytic effects, *I. amara* extract had a tonicising effect in relaxed as well as in slightly contracted ileum (Fig. 4). This effect was significant and

concentration-dependent. The tonicising effects were marginal or lacking in higher acetylcholine concentrations and strongly contracted ileal muscle.

STW 5 is the combination of the drug extracts from STW 7 with the *I. amara* extract. Its spasmolytic effect is comparable or slightly lower than that of STW 7. But in addition, STW 5 has also, like the *I. amara* extract, a tonicising effect in relaxed or slightly contracted intestine (Fig. 4). The concentration–effect curves of STW 5 in the presence of increasing concentrations of acetylcholine (Fig. 1d) therefore can be seen as representing the combined effect of STW 7 and *I. amara* extract, the latter component influencing the slope of the curve especially in the presence of lower concentrations of acetylcholine. Thus it can be concluded that STW 5 has a dual-action mechanism on gastro-intestinal motility, depending on the prevalent patho-physiological condition.

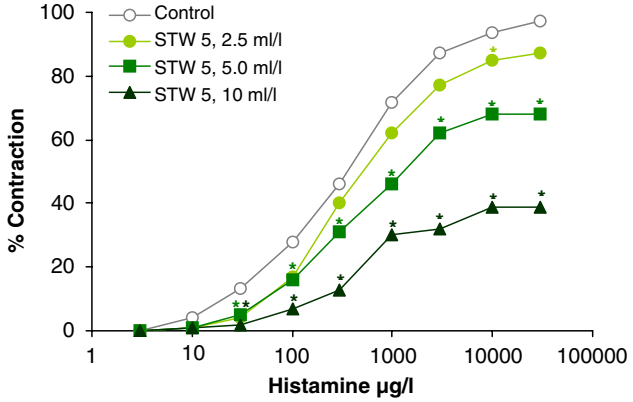

Fig. 3. Effect of STW 5 (Iberogast®) on histamine-induced contraction of isolated guinea pig ileum (100%, values are means ± SEM, $n = 6$, $^{*}p \leqslant 0.01$).

Results from newer studies with STW 5 and its component extracts are in accordance with the results of this study. Heinle et al. (2006) found a spasmolytic effect of STW 5 and several of its components, including *Matricariae flos*, *Menthae folium* and *L. radix*, in guinea pig ileum stimulated with histamine, Hagelauer et al. (2006) also in prostaglandine $F_{2\alpha}$ induced contraction of mouse ileum. Yuece et al. (2006) found a relaxing effect of STW 5 on the peristaltic reflex of mouse ileum. Michael et al. (2006) described a tonicising effect of STW 5 and *I. amara* extract in acetylcholine-stimulated guinea pig ileum after induction of an inflamed state by incubation with 2,4,6 trinitrobenzolsulfonic acid (TNBA), but showed an inhibiting effect of both on

Table 5. Effect of STW 5 (Iberogast®) on histamine-induced contraction of isolated guinea pig ileum

Concentration of test substance (ml/l)	Spasmogen (control) EC_{50} (µg/l)	Spasmogen + test substance, EC_{50} (µg/l)	ΔEC_{50} (µg/l)
1.25	475	310	−165
2.5	400	525	125
5	390	1400	1010*
10	300	>100,000	n.d.**

The EC_{50} are given as histamine concentration in µg/l without and in the presence of STW 5. Data were calculated from curve of Fig. 3. $n = 6$. $^{*}p \leqslant 0.05$; $^{**}p \leqslant 0.01$; n.d. ΔEC_{50} could not be determined.

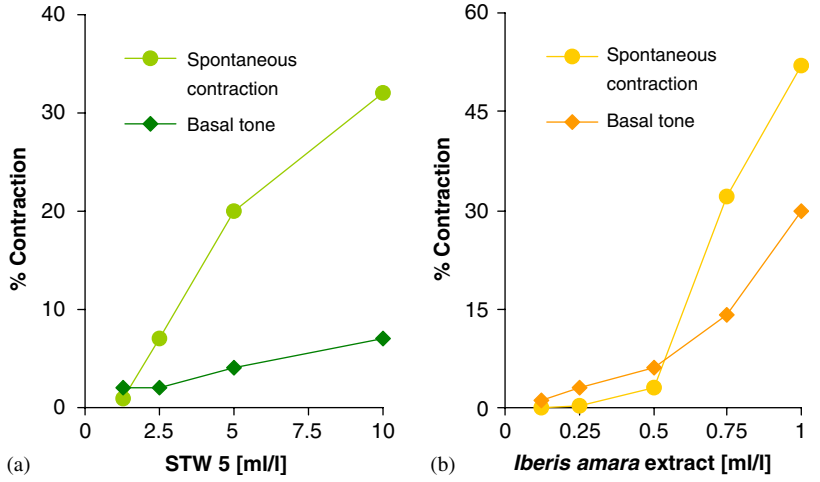

Fig. 4. Effect of (a) STW 5 (Iberogast®) and (b) extract from *Iberis amara* on basal resting tone (absence of acetylcholine) and spontaneous contraction of guinea pig ileum in percent of the contractile effect of acetylcholine (2.56 mg/l; $n = 5$–6).

the spontaneous tone. In gastric muscle, Hohenester et al. (2004) described a region-specific effect of STW 5, acting spasmolytic in gastral corpus and fundus, while tonicising (prokinetic) in gastral antrum. This can be seen as a region-specific form of the dual-action principle, paralleling the dual-action principle shown for the intestinal muscle in this paper. This region-specific effect could be attributed partially to the different effects of the single extracts contained in STW 5 and was reproduced in human gastric muscle in vitro (Schemann et al., 2006). It has now also been verified in man in a clinical pharmacological study (Pilichiewicz et al., 2006).

It can thus be concluded that this dual-action principle of STW 5 (Iberogast®) on gastro-intestinal motility, which depends on the pathophysiological state, and which is represented by a spasmolytic effect in contracted intestinal muscle and a tonicising effect in relaxed muscle, is based on the effects of its components. It is likely to be involved in the clinically proven therapeutic efficacy of STW 5 in functional dyspepsia as well as irritable bowel syndrome (Holtmann et al., 2004; Rösch et al., 2006), which are both diseases with an aetiology to a large extent based on motility disturbances.

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