

Supporting Information

Evaluating the Multitarget Effects of Combinations through Multistep Clustering of Pharmacological Data: the Example of the Commercial Preparation Iberogast

Heba Abdel-Aziz¹, Olaf Kelber¹, Gerhard Lorkowski², Martin Storr³

Affiliation:

¹Phytomedicines Supply and Development Center, Steigerwald Arzneimittelwerk GmbH, Bayer Consumer Health, Darmstadt, Germany; ²GL Pharma Consulting Research & Development, Gauting, Germany; ³Center of Endoscopy, Starnberg and Center of Internal Medicine, Gauting, Germany

Correspondence:

Dr. Heba Abdel-Aziz

Phytomedicines Supply and Development Center
Steigerwald Arzneimittelwerk GmbH

Havelstrasse 5

64295 Darmstadt

Phone: +49 6151 3305 202

Fax: +49 6151 3305 471

heba.abdel-aziz@bayer.com

Table 1S. Fourth order cluster results for STW 5 and its single plant extracts in FD/EPS.

	Acid Regulation	Visceral Hyperhyper-sensitivity	Gastro duodenal Inflammation	Lower Oesophagus Sphincter Pressure	Gastric Accommodation		Mucosal Protection	Total Mean FD / EPS (Mean, Effect Size, Ranking)
					Fundus/Corpus Relaxation	Antrum Contraction		
Reference(s)	[15–17]	[36, 37, 38]	[20, 34, 35]	[14]	[13,14]		[15,16]	
	Mean, Effect Size							
STW 5	2.8 +++ ¹	2.6 +++	2.5 +++	3.0 +++	3.0 +++	2.0 ++	2.5 +++	2.6 +++ (1)
Bitter candy tuft (<i>I. amara</i>)	3.0 +++	2.2 ++	1.4 +	–	- [0] ⁶	2.0 ++	2.0 ++	1.8 ++ (4)
Peppermint (<i>M. piperita</i>)	2.5 +++	–	2.8 +++	–	0 ³	0 ⁴⁵	1.5 ++	1.4 ++ (9)
Chamomile (<i>M. recrutita</i>)	3.0 +++	–	2.6 +++	–	2.0 ++	2.0 ++	2.5 +++	2.4 ++ (2)
Liquorice (<i>G. glabra</i>)	2.5 +++	–	2.2 ++	–	1.0 +	1.0 +	2.0 ++	1.7 ++ (6)
Angelica (<i>A. archangelica</i>)	1.5 ++	–	2.2 ++	–	2.5 +++	2.0 ++	1.5 ++	1.9 ++ (3)
Caraway (<i>C. carvi</i>)	1.5 ++	–	2.4 ++	–	- [0] ⁵	2.0 ++	2.5 +++	1.7 ++ (6)
Milk thistle (<i>S. marianum</i>)	1.0 +	–	2.5 +++	–	0 ³	0 ⁴	3.0 +++	1.3 + (10)
Melissa (<i>M. officinalis</i>)	1.5 ++	–	2.45 ++	–	- [0] ⁵	3.0 +++	1.5 ++	1.7 ++ (6)
Greater celandine (<i>C. majus</i>)	3.0 +++ ²	–	1.2 +	–	- [0] ⁵	3.0 +++	- ²	1.8 ++ (4)²

¹Effect size ranges for mean values from single tests : "+++" = 2.500–3.000; "++" = 1.500–2.499; "+" = <1.500; -[0] = no effect; - = not tested; () = in brackets effect not considered for calculation of means

²Careful interpretation necessary due to lacking data from indomethacin-induced effects.

³Inconsistent results (either contractions or relaxations; tissue-dependent reproducible and dose-dependent; tissues-dependent reverse of response with higher drug concentrations from contraction to relaxation; rather small contractile effects)

⁴Inconsistent effect on antral contractility

⁵Extract induces fundus and corpus contraction instead of relaxation

Table 2S. Fourth order cluster results for STW 5 and its single plant extracts in FD/PDS.

	Gastric Accommodation		Visceral Hyper-sensitivity	Gastroduodenal Inflammation	Mucosal Protection	5-HT Receptors (Nausea)	Total Mean FD / PDS (Mean, Effect Size, Ranking)
	Fundus/Corpus Relaxation	Antrum Contraction					
Reference(s)	[13, 14]		[38]	[15, 16, 20, 34, 35, 48, 23, 24]	[15, 16]	[20, 39]	
	Mean, Effects Size						
STW 5	3.0 +++ ¹	2.0 ++	2.6 +++	2.5 +++	2.5 +++	2.0 ++	2.4 ++ (1)
Bitter candy tuft (<i>I. amara</i>)	- [0] ⁷	2.0 ++	2.2 ++	1.4 +	2.0 ++	1.0 +	1.4 + (7)
Peppermint (<i>M. piperita</i>)	0 ²	0 ⁴	–	2.8 +++	1.5 ++	- [0] ⁵	0.9 + (10)
Chamomile (<i>M. recrutita</i>)	2.0 ++	2.0 ++	–	2.6 +++	2.5 +++	- [0] ⁵	1.8 ++ (3)
Liquorice (<i>G. glabra</i>)	1.0 +	1.0+	–	2.2 ++	2.0 ++	3.0 +++	1.8 ++ (3)
Angelica (<i>A. archangelica</i>)	2.5 +++	2.0 ++	–	2.2 ++	1.5 ++	3.0 +++	2.2 ++ (2)
Caraway (<i>C. carvi</i>)	- [0] ⁷	2.0 ++	–	2.4 ++	2.5 +++	- [0] ⁵	1.4 + (7)
Milk thistle (<i>S. marianum</i>)	0 ²	0 ⁴	–	2.5 +++	3.0 +++	- [0] ⁵	1.1 + (9)
Melissa (<i>M. officinalis</i>)	- [0] ⁶	3.0 +++	–	2.45 ++	1.5 ++	1.0 +	1,6 ++ (6)
Greater celandine (<i>C. majus</i>)	- [0] ⁶	3.0 +++	–	1.2 ++	– ³	3.0 +++	1.8 ++³ (3)

¹Effect size ranges for mean values from single tests: "+++" = 2.500–3.000; "++" = 1.500–2.499; "+" = <1.500; "-[0]" = no effect; "-" = not tested; "()" = in brackets effect not considered for calculation of means

²Inconsistent results (either contractions or relaxations; tissue-dependent reproducible and dose-dependent; tissues-dependent reverse of response with higher drug concentrations from contraction to relaxation; rather small contractile effects)

³Careful interpretation necessary due to lacking data from indomethacin-induced damages

⁴Inconsistent effect on antral contractility (enhanced contraction amplitudes in some fraction, but due to unsteady)

⁵Unspecific binding

⁶Extract induces fundus and corpus contraction instead of relaxation

Table 3S. Fourth order cluster results for STW 5 and its single plant extracts in IBS.

	Intestinal Motility			Mean Intestinal Motility	Visceral Hyper-sensitivity	Intestinal Inflammation	Prosecretory Effect	Mucosal Barrier	Micro-biome	Gas	Total Mean IBS (Mean, Effect Size, Ranking)
	Tonicizing Effect	Neurotransmission	Spasmolytic Effect								
Reference(s)	[41,26,27,32,42]	[30,44]	[26,27,30,41-44]	[26,27,30,32,41-44]	[38]	[25-29, 31,32]	[46]	[15,16]			
	Mean, Effect Size										
STW 5	0.6 +	3.0 +++	2.4 ++	2.0 ++	2.6 +++	1.9 ++	3.0 +++	2.0 ++	-	-	2.2 ++ (1)
Bitter candy tuft (<i>I. amara</i>)	2.3 ++	+↑ ³	(- [0])	1.7 + ³	2.2 ++	1.6 ++	- [0]	1.0 +	-	-	1.3 + (2)
Peppermint (<i>M. piperita</i>)	(- [0]) ¹	- [0]	2.0 ++	1.0 +	-	1.4 +	1.0 +	1.0 + ⁴	-	-	1.1 + (7)
Chamomile (<i>M. recruta</i>)	1.0 +	- [0]	1.1 +	0.7 +	-	1.0 +	1.5 ++	2.0 ++	-	-	1.3 + (2)
Liquorice (<i>G. glabra</i>)	(- [0]) ¹	- [0]	1.7 ++	0.9 +	-	0.7 +	- [0]	2.0 ++	-	-	0.9 + (9)
Angelica (<i>A. archangelica</i>)	(- [0]) ¹	+↓ ³	2.0 ++	1.5 + ³	-	0.8 +	1.5 ++	1.0 + ⁴	-	-	1.2 + (5)
Caraway (<i>C. carvi</i>)	2.0 ++	- [0]	0.5 +	0.8 +	-	1.2 +	- [0]	2.0 ++	-	-	1.0 + (8)
Milk thistle (<i>S. marianum</i>)	1.0 +	- [0]	(- [0])	1.0 +	-	1.0 +	- [0]	3.0 +++	-	-	1.3 + (2)
Melissa (<i>M. officinalis</i>)	(- [0]) ¹	+↓ ³	0.8 +	0.9 + ³	-	1.9 ++	1.0 +	1.0 + ⁴	-	-	1.2 + (5)
Gr. celandine (<i>C. majus</i>)	- [0]	+↓ ³	0.4 +	0.7 + ³	-	1.2 +	- [0]	- ²	-	-	0.6 + (10)²

¹Effect size ranges for mean values from single tests : "+++" = 2.500–3.0; "++" = 1.500–2.499; "+" = <1.500; -[0] = no effect; - = not tested; () = in brackets effect not considered for calculation of means

²Careful interpretation necessary due to lacking data from indomethacin-induced damages

³No(t) (all) quantitative data for categorization available (therefore "1.0" and "+"); negative means inactive; ↓ inhibition of neurotransmission, ↑ stimulation of neurotransmission

⁴Effect size smaller than with 100 mg cimetidine

Table 4S. STW 5 (Iberogast) and its single plant extracts in test systems involved in FD/EPS.

Test System	Acid Regulation				Mean - Acid Regulation (Mean, Effect Size)	Visceral Hyper-sensitivity	Stomach Inflammation					Mean - Stomach Inflammation (Mean, Effect Size)	LESP	Gastric Accommodation		Mucosa Protection		Mean - Mucosa Protection (Mean, Effect Size)	Total Mean FD / EPS (Mean, Effect Size, Ranking)	
	Indomethacin-Induced Ulcer in Male Wistar Rats Cimetidine [100 mg = 100%]	Isolated Partially Purified Guinea-pig Parietal Cell					Male Wistar Rats (Neurovascular bundle of the mesentery in proximal jejunum)	Indomethacin-Induced Ulcer in Male Wistar Rats Cimetidine [100 mg = 100%]	Submean - Indomethacin-Induced Inflammation (Mean, Effect Size)	Different Tests Systems for Antioxidative & Radical Scavenging	Surgical Ligation of Pylorus and Junction in Rats			Isolated Muscle Preparation	Region-Specific Activity on Stomach Motility	Indomethacin-Induced Ulcer in Male Wistar Rats Cimetidine [100 mg = 100%]				
Test Information (e.g., Dose)	Indomethacin in Pyloric-Ligated Rats; 10 mL/kg: STW 5, <i>M. recutita</i> , <i>A. archangelica</i> , <i>S. marianum</i> ; 5 mL/kg: <i>G. glabrata</i> , <i>M. officinalis</i> , 2.5 mL/kg: <i>M. piperita</i> , <i>C. carvi</i> , <i>I. amara</i> .			Histamine- or Dibutylryl cAMP-Stimulated Acid Production Measured by Uptake of 14C-Amidopyrin to the Secretory Canal System	Oral Pretreatment with 10 mL kg ⁻¹ STW 5	Indomethacin in Pyloric-Ligated Rats; 10 mL/kg: STW 5, <i>M. recutita</i> , <i>A. archangelica</i> , <i>S. marianum</i> ; 5 mL/kg: <i>G. glabrata</i> , <i>M. officinalis</i> , 2.5 mL/kg: <i>C. carvi</i> , <i>I. amara</i> .	Submean - Indomethacin-Induced Inflammation (Mean, Effect Size)	Mean Antioxidative & Radical Scavenging Effect		Model of Acute and Chronic Reflux Esophagitis Without Affecting pH or Refluxate	Motility of Guinea Pig LES	(In-Vitro Circular or Longitudinal Axis Muscle Strips from Guinea Pig Stomach)	Indomethacin in Pyloric-Ligated Rats; 10 mL/kg: STW 5, <i>M. recutita</i> , <i>A. archangelica</i> , <i>S. marianum</i> ; 5 mL/kg: <i>G. glabrata</i> , <i>M. officinalis</i> , 2.5 mL/kg: <i>M. piperita</i> , <i>C. carvi</i> , <i>I. amara</i> .							
Test/Variables	Reduction of Gastric Acidity [+ = % Cimetidine] (% <[-]/>[+] Normal: 90 mEq/L)	Reduction of Gastric Acid Output[+ = % Cimetidine] (% <[-]/>[+] Normal: 90 mEq/L)	Reduction [IC ₅₀] of Histamine-Stimulated Acid Production	Reduction [IC ₅₀] of Dibutylryl cAMP-Stimulation	Δ Afferent discharge (imp s ⁻¹)	Increase of Protective Anti-Ulcerogenic Effect (10 mL/kg) [+ = % Cimetidine] (Ulcer Index, Robert, 1967) ^{1,2}		Decrease of Gastric Leukotriene Content [+ = % below indomethacin]	Histological Evaluation	Decrease of Oxidative Effects and Radical Production (+ = % of 100% Induction)	Reduction of Ulcerative Lesion and Others (+ = vs. Induction / Reference)	Reduction of Muscle Tone [Nm];	Mean Reduction Fundus/Corpus Tone (Relaxation) (+ = Reduction from Baseline "0")	Mean Increase of Antrum Contraction Amplitude [+ = % Increase Above Baseline "0"]	Increase of Gastric Mucin Content [+ = % above Indomethacin] Milk thistle = 100% above N	Increase of Gastric PGE ₂ Content [+ = % above Indomethacin]				
Reference(s)	[15, 16]		[17]		[15–17]	[36, 37, 38]	[18, 19]			[15, 16]	[34, 35]	[20]	[15, 16, 20, 34, 35]	[18]	[13, 14]		[15, 16]		[15, 16]	
STW 5	+++ ⁸	+++	+++	++	2.8 +++	2.6 +++	++	+++	++	2.3 ++	2.5 +++	3.0 +++	2.5 +++	3.0 +++	3.0 +++	2.0 ++	++	+++	2.5 +++	2.6 +++ (1)
Bitter candy tuft (<i>I. amara</i>)	+++	+++	+++	+++	3.0 +++	2.2 ++	+++	+++	+++	3.0 +++	1.5 +	–	1.4 +	–	– [0] ⁷	2.0 ++	+	+++	2.0 ++	1.8 ++ (4)
Peppermint (<i>M. piperita</i>)	++	++	+++	+++	2.5 +++	–	+++	+++	–	3.0 +++	2.5 +++	–	2.8 +++	–	0 ⁴	0 ⁵	+ ⁴	++	1.5 ++	1.4 ++ (9)
Chamomile (<i>M. recutita</i>)	+++	+++	+++	+++	3.0 +++	–	++	+++	+++	2.7 +++	2.5 +++	–	2.6 +++	–	2.0 ++	2.0 ++	++	+++	2.5 +++	2.4 ++ (2)
Liquorice (<i>G. glabra</i>)	++	++	+++	+++	2.5 +++	–	+++	+++	–	3.0 +++	1.4 +	–	2.2 ++	–	1.0 +	1.0+*	++	++	2.0 ++	1.7 ++ (6)
Angelica (<i>A. archangelica</i>)	+++	+++	– [0] ³	– [0] ³	1.5 ++	–	++	+++	–	2.5 +++	1.7 ++	–	2.2 ++	–	2.5 +++	2.0 ++	+ ⁴	++	1.5 ++	1.9 ++ (3)
Caraway (<i>C. carvi</i>)	+++	+++	– [0] ³	– [0] ³	1.5 ++	–	+++	+++	–	3.0 +++	1.7 ++	–	2.4 ++	–	– [0] ⁷	2.0 ++	++	+++	2.5 +++	1.7 ++ (6)
Milk thistle (<i>S. marianum</i>)	++	++	– [0] ³	– [0] ³	1.0 +	–	+++	+++	–	3.0 +++	2.0 ++	–	2.5 +++	–	0 ⁴	0 ⁵	+++	+++	3.0 +++	1.3 + (10)
Melissa (<i>M. officinalis</i>)	+++	+++	– [0] ³	– [0] ³	1.5 ++	–	++	+++	++	2.3 ++	2.6 +++	–	2.45 ++	–	– [0] ⁷	3.0 +++	+ ⁴	++	1.5 ++	1.7 ++ (6)
Gr.celandine herb (<i>C. majus</i>)	–	–	+++	+++	3.0 ++ ⁹	–	–	–	–	–	1.8 ++	–	1.2 ++	–	– [0] ⁷	3.0+++	–	–	–	1.8 ++ (4) ⁹

¹Ulcer-Index acc. to Robert, 1967

²About 10% above protective effect of 100 mg cimetidine

³None or only weak inhibitory effect; no IC₅₀ possible with 10 µL extract

⁴Effect size below 100 mg cimetidine

⁵Decrease of normal value by 50%.

⁶Effect size only slightly below normal

⁷Data not assessable

⁸Effect size ranges for mean values from single tests : "+++ " = 2.500–3.000; "++ " = 1.500–2.499; "+" = <1.500; "- [0]" = no effect; "- " = not tested; "()" = in brackets effect not considered for calculation of means

⁹Careful interpretation necessary due to lacking data from indomethacin-induced damages

¹⁰Inconsistent results (either contractions or relaxations; tissue-dependent reproducible and dose-dependent; tissues-dependent reverse of response with higher drug concentrations from contraction to relaxation; rather small contractile effects)

Table 5S: STW 5 (Iberogast) and its single plant extracts in test systems involved in FD/PDS.

Test system	Gastric Accommodation		Mean Fundus / Corpus Relaxation	Increase of Antrum Contraction Amplitude [+ = % Increase Above Baseline "0"]	Mean - Hypersensitivity / Pain Mean, (Effect Size)	Inflammation (Stomach / Duodenum)													Mean - Inflammation (Stomach / Duodenum) (Mean, Effect Size)	Mean - Mucosa Protection (Mean, Effect Size)	5-HT-Receptors (Nausea)		Mean 5-HT (Mean, Effect Size)	Total Mean FD/PDS (Mean, Effect Size, Ranking)
	Region-specific Activity on Stomach Motility	In-Vitro Circular or Longitudinal Axis Muscle Strips from Guinea Pig Stomach ¹				Indomethacin-Induced Inflammation	Different Tests Systems for Anti-oxidative & Radical Scavenging	Surgical Ligation Pylorus and Junction in Rats	Inflammation in Distal (Ileum/Jejunum) Small Intestine of Male Wistar Rats			Adenosine Receptor Binding		TNBS-induced suppression of Adenosine Receptor mRNA			Rat Intestinal 5-HT ₃ -Receptors	Guinea Pig Ileum - 5-HT ₃ - and neurokinin receptor s						
Test information (e.g. Dose)						Mean Anti-Inflammatory Effect (Ulcer Index, Gastric Leukotriene, Histology)	Mean Anti-oxidative & Radical Scavenging Effect	Mean Model of Acute and Chronic Reflux Esophagitis Without Affecting pH or Refluxate	TNBs-Induced Inflammation/Damage			LPS-induced TNFα Release from Human Monocytes	Rat Cortical Tissue Homogenates for Adenosine A ₁ Receptor	Rat Striatal Tissue Homogenates for Adenosine A _{2A} Receptor	Adenosine Receptor A ₁ mRNA	Adenosine Receptor A _{2A} mRNA	Adenosine Receptor A ₃ mRNA		Binding Affinity					
Test/ variables	Reduction Fundus Tone (Relaxation) (+ = Reduction from Baseline "0")	Reduction Corpus Tone (Relaxation) (+ = Reduction from Baseline "0")				Decrease Ulcer Index (Ulcer Protection, Gastric Leukotriene, Histology)	Decrease of Oxidative Effects and Radical Production (+ = % of 100% Induction)	Reduction of Ulcerative Lesion and Others (vs. Induction / Reference)	Concentration-Dependent Reduction [%] of TNBS-Induced Decrease of ACh-Induced Contraction (Damage)	Protection of TNBS-Induced Damage (Mucosal Layer, Sub-mucosal Muscular Layer, Villus Height) [% Size] by Co-Incubation	Relative Unit Increase of IL-10 Gene Expression Above Control & TNBS (Without Influence)	Relative Unit Decrease of TNFα Gene Expression	Relative Unit Decrease of TNFα Release ³	Displacement of the Radioactive-Labeled Specific Agonist [%]		Increase of Relative Units of mRNA after Co-Incubation of TNBS (10 mM, 30 min.) and STW5 or Single Extract			IC ₅₀ Extract Dilution	Reduction [%] of Effector-Induced Contraction				
Reference(s)	[13,18]		[13,18]	[36,37,38]	[15,116]	[34,35]	[20]	[23]					[24]					[15,16,20,23,24,34,35]	[15,16]	[39]	[40]	[39,40]		
STW5	+++ ⁶	+++	3.0 +++	2.0 ++	2.6 +++	2.3 ++	2.5 +++	3.0 +++	+	+++	++	++*	+++	+++	+++	+	+++	+	2.5 +++	2.5 +++	+	+++	2.0 ++	2.4 ++ (1)
Bitter candy tuft (<i>I. amara</i>)	- [0] ⁷	- [0] ⁷	- [0] ⁷	2.0 ++	2.2 ++	3.0 +++	1.5 ++	-	++	+++	+++	- [0]*	- [0]	+/- ²	+/- ²	-	-	-	1.4 +	2.0 ++	+	-	1.0 +	1.4 + (7)
Peppermint (<i>M. piperita</i>)	0 ⁴	0 ⁴	0 ⁴	0 ⁵	-	3.0 +++	2.5 ++	-	-	-	-	-	-	-	-	-	-	-	2.8 +++	1.5 ++	- [0] ²	-	- [0] ²	0.9 + (10)
Chamomile (<i>M. recutita</i>)	++	++	2.0 ++	2.0 ++	-	2.7 +++	2.5 +++	-	-	-	-	-	-	-	-	-	-	-	2.6 +++	2.5 +++	- [0] ²	-	- [0] ²	1.8 ++ (3)
Liquorice (<i>G. glabra</i>)	+	+	1.0 +	1.0+	-	3.0 +++	1.4 +	-	-	-	-	-	-	-	-	-	-	-	2.2 ++	2.0 ++	+++	-	3.0 +++	1.8 ++ (3)
Angelica (<i>A. archangelica</i>)	+++	++	2.5 +++	2.0 ++	-	2.5 +++	1.7 ++	-	-	-	-	-	-	-	-	-	-	-	2.2 ++	1.5 ++	+++	-	3.0 +++	2.2 ++ (2)
Caraway (<i>C. carvi</i>)	- [0] ⁷	- [0] ⁷	- [0] ⁷	2.0 ++	-	3.0 +++	1.7 ++	-	-	-	-	-	-	-	-	-	-	-	2.4 ++	2.5 +++	- [0] ²	-	- [0] ²	1.4 + (7)
Milk thistle (<i>S. marianum</i>)	0 ⁴	0 ⁴	0 ⁴	0 ⁵	-	3.0 +++	2.0 ++	-	-	-	-	-	-	-	-	-	-	-	2.5 +++	3.0 +++	- [0] ²	-	- [0] ²	1.1 + (9)
Melissa (<i>M. officinalis</i>)	- [0] ⁷	- [0] ⁷	- [0] ⁷	3.0 +++	-	2.3 ++	2.6 +++	-	-	-	-	-	-	-	-	-	-	-	2.45 ++	1.5 ++	+	-	1.0 +	1.6 ++ (6)
Greater celandine (<i>C. majus</i>)	- [0] ⁷	- [0] ⁷	- [0] ⁷	3.0 +++	-	-	1.8 ++	-	- [0]	-	-	-	+++	++ ²	++ ²	-	-	-	1.2 ++ ⁸	- ⁸	+++	-	3.0 +++	1.8 ++ (3) ⁸

¹Amount of extracts used: 10 mL/kg: STW 5, *M. recutita*, *A. archangelica*, *S. marianum*; 5 mL/kg: *G. glabra*, *M. officinalis*, 2.5 mL/kg: *M. piperita*, *C. carvi*, *I. amara*.

²Unspecific binding

³No effects of STW 5 and STW 6 on basal TNF-α release

⁴Inconsistent results (either contractions or relaxations; tissue-dependent reproducible and dose-dependent; tissues-dependent reverse of response with higher drug concentrations from contraction to relaxation; rather small contractile effects)

⁵Inconsistent effect on antral contractility (enhanced contraction amplitudes in some fraction, but due to unsteady nature and lack of concentration-dependency no statistical significance reached)

⁶Effect size ranges for mean values from single tests: "+++ = 2.500–3.000; "++ = 1.500–2.499; "+" = 0–1.499; "- [0]" = no effect; "-" = not tested;

⁷Extract induces fundus and corpus contraction; () = in brackets effect not considered for calculation of means

⁸Careful interpretation necessary due to lacking data from indomethacin-induced damages

