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.

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Acid Regulation</th>
<th>Visceral Hyper-sensitivity</th>
<th>Gastro duodenal Inflammation</th>
<th>Lower Oesophagus Sphincter Pressure</th>
<th>Gastric Accommodation</th>
<th>Mucosal Protection</th>
<th>Total Mean FD / EPS (Mean, Effect Size, Ranking)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STW 5</td>
<td>2.8 +++&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.6 ++</td>
<td>2.5 +++</td>
<td>3.0 +++</td>
<td>3.0 +++</td>
<td>2.0 ++</td>
<td>2.5 +++</td>
</tr>
<tr>
<td>Bitter candy tuft (I. amara)</td>
<td>3.0 +++</td>
<td>2.2 ++</td>
<td>1.4 +</td>
<td>_</td>
<td>- [0]&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2.0 ++</td>
<td>2.0 ++</td>
</tr>
<tr>
<td>Peppermint (M. piperita)</td>
<td>2.5 +++</td>
<td>_</td>
<td>2.8 +++</td>
<td>_</td>
<td>0&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0&lt;sup&gt;13&lt;/sup&gt;</td>
<td>1.5 ++</td>
</tr>
<tr>
<td>Chamomile (M. recrutita)</td>
<td>3.0 +++</td>
<td>_</td>
<td>2.6 +++</td>
<td>_</td>
<td>2.0 ++</td>
<td>2.0 ++</td>
<td>2.5 +++</td>
</tr>
<tr>
<td>Liquorice (G. glabra)</td>
<td>2.5 +++</td>
<td>_</td>
<td>2.2 ++</td>
<td>_</td>
<td>1.0 +</td>
<td>1.0 +</td>
<td>2.0 ++</td>
</tr>
<tr>
<td>Angelica (A. archangelica)</td>
<td>1.5 ++</td>
<td>_</td>
<td>2.2 ++</td>
<td>_</td>
<td>2.5 +++</td>
<td>2.0 ++</td>
<td>1.5 ++</td>
</tr>
<tr>
<td>Caraway (C. carvi)</td>
<td>1.5 ++</td>
<td>_</td>
<td>2.4 ++</td>
<td>_</td>
<td>- [0]&lt;sup&gt;7&lt;/sup&gt;</td>
<td>2.0 ++</td>
<td>2.5 +++</td>
</tr>
<tr>
<td>Milk thistle (S. marianum)</td>
<td>1.0 +</td>
<td>_</td>
<td>2.5 +++</td>
<td>_</td>
<td>0&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0&lt;sup&gt;14&lt;/sup&gt;</td>
<td>3.0 +++</td>
</tr>
<tr>
<td>Melissa (M. officinalis)</td>
<td>1.5 ++</td>
<td>_</td>
<td>2.45 ++</td>
<td>_</td>
<td>- [0]&lt;sup&gt;7&lt;/sup&gt;</td>
<td>3.0 +++</td>
<td>1.5 ++</td>
</tr>
<tr>
<td>Greater celandine (C. majus)</td>
<td>3.0 +++&lt;sup&gt;2&lt;/sup&gt;</td>
<td>_</td>
<td>1.2 +</td>
<td>_</td>
<td>- [0]&lt;sup&gt;5&lt;/sup&gt;</td>
<td>3.0 +++</td>
<td>_</td>
</tr>
</tbody>
</table>

<sup>1</sup>Effect 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

<sup>2</sup>Careful interpretation necessary due to lacking data from indomethacin-induced effects.

<sup>3</sup>Inconsistent 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)

<sup>4</sup>Inconsistent effect on antral contractility.

<sup>5</sup>Extract 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.

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

1 Effect size ranges for mean values from single tests: "+++" = 2.500–3.000; "++" = 1.500–2.499; "+" = ≤1.500; "-" = no effect; "-" = not tested; () = in brackets effect not considered for calculation of means
2 Inconsistent 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)
3 Careful interpretation necessary due to lacking data from indomethacin-induced damages
4 Inconsistent effect on antral contractility (enhanced contraction amplitudes in some fraction, but due to unsteady)
5 Unspecific binding
6 Extract induces fundus and corpus contraction instead of relaxation

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

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Intestinal Motility</th>
<th>Mean Intestinal Motility</th>
<th>Visceral Hyper-sensitivity</th>
<th>Intestinal Inflammation</th>
<th>Prosecretory Effect</th>
<th>Mucosal Barrier</th>
<th>Microbiome</th>
<th>Gas</th>
<th>Total Mean IBS (Mean, Effect Size, Ranking)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[41,26,27,32,42]</td>
<td>[30,44]</td>
<td>[26,27,30,41-44]</td>
<td>[26,27,30,32,41-44]</td>
<td>[38]</td>
<td>[25-29,31,32]</td>
<td>[46]</td>
<td>[15,16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STW 5</strong></td>
<td>0.6 +</td>
<td>3.0 +++</td>
<td>2.4 ++</td>
<td>2.0 ++</td>
<td>2.6 +++</td>
<td>1.9 ++</td>
<td>3.0 +++</td>
<td>2.0 ++</td>
<td>_</td>
</tr>
<tr>
<td><strong>Bitter candy tuft (I. amara)</strong></td>
<td>2.3 ++</td>
<td>+↑↑</td>
<td>(- [0])</td>
<td>1.7 +↑</td>
<td>2.2 ++</td>
<td>1.6 ++</td>
<td>- [0]</td>
<td>1.0 +</td>
<td>_</td>
</tr>
<tr>
<td><strong>Peppermint (M. piperita)</strong></td>
<td>(- [0])</td>
<td>- [0]</td>
<td>2.0 ++</td>
<td>1.0 +</td>
<td>_</td>
<td>1.4 +</td>
<td>1.0 +</td>
<td>1.0 +↑</td>
<td>_</td>
</tr>
<tr>
<td><strong>Chamomile (M. recutita)</strong></td>
<td>1.0 +</td>
<td>- [0]</td>
<td>1.1 +</td>
<td>0.7 +</td>
<td>_</td>
<td>1.0 +</td>
<td>1.5 ++</td>
<td>2.0 ++</td>
<td>_</td>
</tr>
<tr>
<td><strong>Liquorice (G. glabra)</strong></td>
<td>(- [0])</td>
<td>- [0]</td>
<td>1.7 ++</td>
<td>0.9 +</td>
<td>_</td>
<td>0.7 +</td>
<td>- [0]</td>
<td>2.0 ++</td>
<td>_</td>
</tr>
<tr>
<td><strong>Angelica (A. archangelica)</strong></td>
<td>(- [0])</td>
<td>+↓↓</td>
<td>2.0 ++</td>
<td>1.5 +↑</td>
<td>_</td>
<td>0.8 +</td>
<td>1.5 ++</td>
<td>1.0 +↑</td>
<td>_</td>
</tr>
<tr>
<td><strong>Caraway (C. carvi)</strong></td>
<td>2.0 ++</td>
<td>- [0]</td>
<td>0.5 +</td>
<td>0.8 +</td>
<td>_</td>
<td>1.2 +</td>
<td>- [0]</td>
<td>2.0 ++</td>
<td>_</td>
</tr>
<tr>
<td><strong>Milk thistle (S. marianum)</strong></td>
<td>1.0 +</td>
<td>- [0]</td>
<td>(- [0])</td>
<td>1.0 +</td>
<td>_</td>
<td>1.0 +</td>
<td>- [0]</td>
<td>3.0 +++</td>
<td>_</td>
</tr>
<tr>
<td><strong>Melissa (M. officinalis)</strong></td>
<td>(- [0])</td>
<td>+↓↓</td>
<td>0.8 +</td>
<td>0.9 +↑</td>
<td>_</td>
<td>1.9 ++</td>
<td>1.0 +</td>
<td>1.0 +↑</td>
<td>_</td>
</tr>
<tr>
<td><strong>Gr. celandine (C. majus)</strong></td>
<td>- [0]</td>
<td>+↓↓</td>
<td>0.4 +</td>
<td>0.7 +↑</td>
<td>_</td>
<td>1.2 +</td>
<td>- [0]</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

1 Effect 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
2 Careful interpretation necessary due to lacking data from indomethacin-induced damages
3 Not all quantitative data for categorization available (therefore "1.0" and "+"); negative means inactive; ↓ inhibition of neurotransmission, ↑ stimulation of neurotransmission
4 Effect size smaller than with 100 mg cimetidine
<table>
<thead>
<tr>
<th>Test System</th>
<th>Acid Regulation</th>
<th>Visceral Hypersensitivity</th>
<th>Stomach Inflammation</th>
<th>LESP</th>
<th>Gastric Accommodation</th>
<th>Mucoza Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indomethacin-Induced Ulcer in Male Wistar Rats Cimetidine [100 mg = 100%]</td>
<td>Male Wistar Neurally bundled of the mesentery in proximal jejunum</td>
<td>Indomethacin-Induced Ulcer in Male Wistar Rats Cimetidine [100 mg = 100%]</td>
<td>Different Tests for Antioxidant &amp; Radical Scavenging</td>
<td>Suprachelic Ligation of pylorus and injection in Rats</td>
<td>Isolated Muscle Preparation</td>
</tr>
<tr>
<td>Test Information</td>
<td>Indomethacin in Pyloric-Ligated Rats, 10 ml/kg STW 5, M. archangelica, S. marianum, 5 ml/kg, G. glabra, M. officinalis, 2.5 ml/kg, M. piperita, C. carvi, I. amara.</td>
<td>Oral Pre-treatment with 10 ml STW 5</td>
<td>Indomethacin in Pyloric-Ligated Rats, 10 ml/kg STW 5, M. archangelica, S. marianum, 5 ml/kg, G. glabra, M. officinalis, 2.5 ml/kg, M. piperita, C. carvi, I. amara.</td>
<td>Mean - Stomach Inflammation (Mean, Effect Size)</td>
<td>Mean - Stomach Inflammation (Mean, Effect Size)</td>
<td>Motility of Guinea Pig LES</td>
</tr>
<tr>
<td>Test/Variables</td>
<td>Reduction of Gastric Acid (as % Cimetidine) [%, %]</td>
<td>Reduction of Gastric Acid Output [%, %]</td>
<td>Histamine- or Dibutyryl cAMP-Stimulated Acid Production</td>
<td>Reduction of Gastric Acid Production</td>
<td>Reduction of Histamine-stimulated Acid Production [C(0)] or Dibutyryl cAMP-Stimulation</td>
<td>Increase of Protective Antioxidant Effect (IC50 [mL] /% Cimetidine)</td>
</tr>
<tr>
<td>Reference(s)</td>
<td>[15, 16, 17]</td>
<td>[15-17]</td>
<td>[36, 37, 38]</td>
<td>[18, 19]</td>
<td>[15, 16, 34, 35]</td>
<td>[20]</td>
</tr>
<tr>
<td>STW 5</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Ritter candy tuft (J. amara)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Pepperseed (M. piperita)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
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<td>++++</td>
</tr>
<tr>
<td>Chamomilla (M. recutita)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Liquiritica (G. glabra)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Angelica (A. archangelica)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Caraway (K. carvi)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Multhistle (S. marianum)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Melissa (M. officinalis)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Gre. celandine herb (C. majus)</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

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; tissue-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.

<table>
<thead>
<tr>
<th>Test system</th>
<th>Gastric Accommodation</th>
<th>Test information (e.g. Dose)</th>
<th>Test variables</th>
<th>Gastric Sensitivity</th>
<th>Indomethacin Induced Inflammation</th>
<th>Inflammation (Stomach / Duodenum)</th>
<th>5-HT-Receptors (Nanomolar)</th>
<th>S-Heptalin (Mean, Effect Size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region-specific Activity on Stomach Motility</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>In-vitro Circular or Longitudinal Axis Muscle Stips from Guinea Pig Stomach</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean Fundus / Corpus Relaxation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean - Hypercontractility / Pain Mean, (Effect Size)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase of Antrum Contractility Amplitude (+ = Increase Above Baseline [0])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Inflammatory Inflammation (Stomach / Duodenum)**

1. **Peppermint**
   - **M. officinalis**: Unspecific binding
   - **M. piperita**: Inconsistent effect on antral contractility (enhanced contraction amplitudes in some fraction, but due to unsteady nature and lack of concentration its single plant extracts in test systems involved in FD/PDS)

2. **Oregano**
   - **M. piperita**: Inconsistent inhibition of ACh-induced contraction in rat stomach and corpus
   - **M. officinalis**: Decrease of Oxidative Effects and Radial Production (+ = Increase of 100% Induction)

3. **Chamomile**
   - **M. chamaemelum**: Relative Unit Decrease of TNF-α Expression
   - **M. recutita**: Reduction of ulcerative lesion and others in induction/recovery

4. **Liquorice**
   - **G. glabra**: Relative Unit Decrease of TNF-α Expression

5. **Angelica**
   - **A. archangelica**: Relative Decrease of TNF-α Expression

6. **Caraway**
   - **C. carvi**: Relative Decrease of TNF-α Expression

7. **Nutmeg**
   - **D. aromatica**: Relative Decrease of TNF-α Expression

8. **Greater celandine**
   - **C. majus**: Relative Decrease of TNF-α Expression

**Table 5S Reference(s)**

1. [36,37,38]
2. [39,40]

**Table 5S Methodology**

2. Unspecific binding
3. No effects of STW 5 and STW 6 on basal T NF-α release
4. Inconsistent results (either contractions or relaxations; tissue-dependent reproducible and dose-dependent; tissues-dependent response of reversal with higher drug concentrations from contraction to relaxation; rather small contractile effects)
5. Inconsistent effect on antral contractility (enhanced contraction amplitudes in some fraction, but due to unsteady nature and lack of concentration-dependency no statistical significance reached)
6. Effect size ranges for mean values from single tests: *"+* = 2.500-3.000; *"++* = 1.500-2.499; *"+++* = 0.1-1.499; [0] = no effect, = not tested.
7. Extract induces fundus and corpus contraction; (1) = in brackets effect not considered for calculation of means
8. Careful interpretation necessary due to lacking data from indomethacin-induced damages

<table>
<thead>
<tr>
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<th>Test Variables</th>
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<th>Gastrointestinal Motility</th>
<th>Neuroendocrine Effects</th>
<th>Immunological Effects</th>
<th>Microbiological Effects</th>
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*Table 6S. STW 5 (Iberogast) and its single plant extracts in test systems involved in IBS.*