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ORIGINAL ARTICLE

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The herbal preparation, STW5-II, reduces proximal gastric tone and stimulates antral pressures in healthy humans

Penelope C. E. Fitzgerald[1] | Vida Bitarafan[1] | Taher Omari[2] | Charles Cock[2] | Karen L. Jones[1,3] | Michael Horowitz[1,3] | Christine Feinle-Bisset[1]

[1]Adelaide Medical School and Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, South Australia, Australia

[2]Department of Gastroenterology and Hepatology, College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia

[3]Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence
Christine Feinle-Bisset, Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, SA 5005, Australia.
Email: christine.feinle@adelaide.edu.au

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Abstract

Background: The herbal preparation, STW5-II, improves upper gastrointestinal symptoms, including abdominal fullness, early satiation, and epigastric pain, in patients with functional dyspepsia, and in preclinical models decreases fundic tone and increases antral contractility. The effects of STW5-II on esophago-gastric junction pressure, proximal gastric tone and antropyloroduodenal pressures, disturbances of which may contribute to symptoms associated with disorders of gut–brain interaction, including functional dyspepsia, in humans, have, hitherto, not been evaluated.

Methods: STW5-II or placebo (matched for color, aroma, and alcohol content) were each administered orally, at the recommended dose (20 drops), to healthy male and female volunteers (age: 27 ± 1 years) in a double-blind, randomized fashion, on two separate occasions, separated by 3–7 days, to evaluate effects on (i) esophago-gastric junction pressures following a standardized meal using solid-state high-resolution manometry (part 1, $n = 16$), (ii) proximal gastric volume using a barostat (part 2, $n = 16$), and (iii) antropyloroduodenal pressures assessed by high-resolution manometry (part 3, $n = 18$), for 120 min (part 1) or 180 min (parts 2, 3).

Key Results: STW5-II increased maximum intrabag volume (ml; STW5-II: 340 ± 38, placebo: 251 ± 30; $p = 0.007$) and intrabag volume between $t = 120$ and 180 min ($p = 0.011$), and the motility index of antral pressure waves between $t = 60$ and 120 min ($p = 0.032$), but had no effect on esophago-gastric junction, pyloric, or duodenal pressures.

Conclusions & Inferences: STW5-II has marked region-specific effects on gastric motility in humans, which may contribute to its therapeutic efficacy in functional dyspepsia.

KEYWORDS
gastrointestinal, gut motor functions, herbal preparation, human, lower esophageal sphincter, stomach

1 | INTRODUCTION

Functional dyspepsia is a clinical syndrome characterized by chronic, or recurrent, upper gastrointestinal (GI) symptoms in the absence of a clearly identifiable cause. Approximately 5%–20% of the adult population globally is affected, with consequent major socioeconomic implications. Characteristic symptoms include bothersome abdominal fullness, early satiation, and epigastric pain.[1,2] Functional dyspepsia is associated with a number of upper gastrointestinal dysfunctions, including disordered gastric emptying[1,3–5] and intragastric meal distribution,[6] impaired relaxation of the proximal stomach,[7–9] antral dysmotility,[10] and hypersensitivity to gastric distension[11–13] and intraduodenal nutrients, particularly fat.[7,14] Abnormal intragastric meal distribution is intuitively indicative of either defective postprandial relaxation of the proximal stomach[9] and/or dysfunction of the distal stomach.[10] Functional dyspepsia patients with impaired proximal gastric accommodation experience more postprandial symptoms.[8]

There has been, and continues to be, considerable interest in phytotherapy as a treatment option for symptoms associated with disorders of gut–brain interaction, including functional dyspepsia, particularly given the absence of effective pharmacotherapy. The herbal preparations, STW5 and STW5-II (Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany), have been shown to be effective at improving GI symptoms in functional dyspepsia,[15–23] but without the adverse effects of pharmaceutical drugs, including metoclopramide and cisapride,[16,18,24] with the latter withdrawn from the market in 2000 due to its cardiotoxic effects. STW5-II consists of six herbal extracts (bitter candy tuft, camomile flower, caraway fruit, melissa leaf, peppermint leaf, and licorice root), thus, excluding three herbs (angelica root, milk thistle fruit, and greater celandine herb) present in STW5,[25] and, accordingly, comprising a less complex formulation.

In guinea pig and human tissue preparations, both STW5 and STW5-II modulate gastric contractility in a region-specific manner, decreasing fundic tone and stimulating antral contractility.[25–27] In an ex vivo study of a lower esophageal sphincter preparation, STW5 was reported to increase lower esophageal sphincter tone,[28] suggesting that it may be useful in the management of gastro-esophageal reflux. We have previously shown in healthy humans[29] that, consistent with the outcomes of preclinical studies, STW5 reduced proximal gastric tone and increased contractility of the antrum. STW5-II, as discussed, is devoid of angelica, which relaxes the fundus and increases antral contractility, as well as greater celandine and milk thistle extracts, which stimulate both fundic and antral contractility,[25] but still contains licorice root and chamomile flower (and in a higher concentration than STW5), both with fundus-relaxing and antrum-stimulatory effects. There is no information about the effects of STW5-II on the lower esophageal sphincter, proximal gastric tone, and antropyloroduodenal pressures in humans, and whether these compare with those of STW5, despite its differing composition. Knowledge of the upper GI motor effects of STW5-II would provide insights into the mechanisms that may contribute to the clinical efficacy and the potential for 'personalized' use of this preparation.

Key points

- The herbal preparation, STW5-II, potently reduces gastric tone (measured as an increase in the volume within a barostat bag positioned in the proximal stomach), and increased the antral motility index, in healthy volunteers.
- STW5-II did not affect pressures in the esophago-gastric junction, pylorus or duodenum.
- The relationship(s) between the observed changes in gastric functions and the established effects of STW5-II to improve GI symptoms in patients with functional dyspepsia warrant(s) evaluation.

The aims of the current study were, therefore, to determine the acute effects of STW5-II on esophago-gastric junction pressure, proximal gastric tone, and antropyloroduodenal motility in healthy humans. Based on preclinical findings, the hypothesis was that STW5-II would increase esophago-gastric junction pressure, proximal gastric tone, and antral contractility.

2 | METHODS

2.1 | Study participants

Healthy, normal-weight men and women aged 18–60 years were included to establish physiological effects of the treatment. Participant recruitment is detailed in Figure 1. Four participants completed three study parts and eight completed two parts. Participants were recruited by advertisement from the general community and screened before their inclusion to exclude GI symptoms and a history of GI disease or surgery, vegetarians, smokers, alcohol consumption of >2 drinks (20 g ethanol) on >5 days/week, use of medications known to affect GI function, high-performance athletes, allergy or known intolerance to any STW5-II ingredients, unstable body weight (≥5% change over the 3 months before participation), and an inability to comprehend the study protocol. Women were not taking hormonal contraception and had a negative pregnancy test before their inclusion. All participants provided written informed consent. The study protocol was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network (CALHN Reference Number 13450) and performed in accordance with the Declaration of Helsinki. Each study part was registered as a clinical trial with the Australian New Zealand Clinical Trials Registry https://www.anzctr.org.au/ ACTRN12621000480886 (part 1), ACTRN12621000149864 (part 2), and ACTRN12621000116820 (part 3).

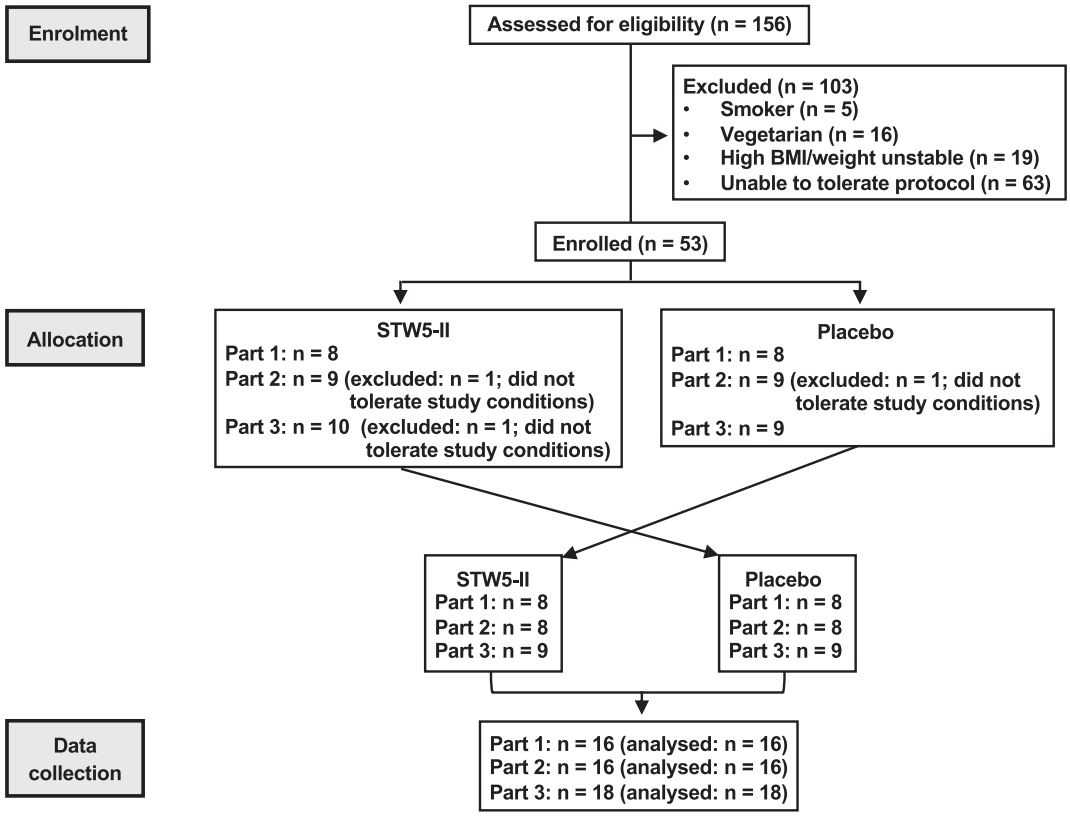

FIGURE 1 CONSORT flow diagram.

2.2 | Study design

This double-blind, randomized, crossover study evaluated the effects of STW5-II, or placebo, on esophago-gastric junction pressure (part 1), proximal gastric tone (part 2), and pressures in the antropyloroduodenal region (part 3).

2.3 | Study treatments

STW5-II contains six plant extracts, including fresh plant extract of *Iberis amara* L. (bitter candytuft), *Matricaria chamomilla* L. (camomile flower), *Carum carvi* L. (caraway fruit), *Melissa officinalis* L. (balm leaf), *Mentha piperita* L. (peppermint leaf), and *Glyrrhiza glabra* L. (licorice root), in 31% ethanol, and the placebo treatment was matched for color, aroma, and alcohol content, ensuring blinding of both the participant and investigator. Both were provided by Steigerwald and administered at the recommended dose of 20 drops (~1.1 mL). Solutions were drawn into a syringe, injected into the participant's mouth, and washed down with 50 mL of water at room temperature.

2.4 | Study protocol

For each part, participants were studied on two occasions separated by 3–7 days in randomized, double-blind fashion. The randomization, provided by Steigerwald, was conducted using the sequential numbered method in chronological order of admission, with respective code-breaking cards available. Premenopausal women were studied during the follicular phase of their menstrual cycle, that is, between days 1 and 8. Participants were instructed to refrain from strenuous exercise and alcohol consumption for 24 h before each study visit and provided with a standardized meal (beef lasagne, 400 g: total energy content: 1160 kcal; McCain Food, Wendouree, Victoria, Australia) to be consumed between 6 and 7 p.m. the night before each study visit, after which they were instructed to refrain from eating and drinking, except water (which was allowed until 7 a.m.). On the morning of the study, the participant attended either the Gut Function Laboratory, Flinders University, Flinders Medical Centre, at 9 a.m. (for study part 1), or the Clinical Research Facility, Adelaide Medical School, University of Adelaide, at 8 a.m. (for study parts 2 and 3).

2.4.1 | Part 1: Effects on esophago-gastric junction pressure

Sixteen participants (11 M/5F, mean age: 25 ± 2 years, BMI: 22.2 ± 0.4 kg/m^2) were included. Following arrival in the laboratory, an 8 French (outer diameter: 2.5 mm) solid-state unidirectional high-resolution manometry catheter (32 pressure sensors at 1-cm intervals, 16 2-cm length impedance segments, Unisensor/Laborie, Attikon, Switzerland) was inserted through an anesthetized nostril and advanced until the pressure array straddled

the esophago-gastric junction from the distal esophagus to the stomach as per routine clinical manometry.[30] After a 10-min period (to accustom the participant to the presence of the catheter), baseline esophago-gastric junction pressure was recorded for 10 min ($t = -15$ to -5 min). At $t = -5$ min, the participant received either STW5-II or placebo and then consumed a mixed solid–liquid meal within 5 min. The meal consisted of a 100-g minced beef burger (270 kcal, 25 g protein, 21 g fat) and 150 mL dextrose solution (10%, 62 kcal). The time of meal completion was defined as $t = 0$ min, and esophago-gastric junction pressures were measured for the following 120 min ($t = 0$ to 120 min). Evaluations were limited to 120 min in this part for logistical reasons. At $t = 120$ min, the manometric assembly was removed, and the participant was offered a light lunch before leaving the laboratory.

2.4.2 | Part 2: Effects on proximal gastric volumes

Sixteen participants (16 M, mean age: 28 ± 2 years, BMI: 23.0 ± 0.7 kg/m^2) completed this part. Following arrival, participants were intubated with a single-lumen silicon oro-gastric catheter (outer diameter: 4 mm, inner diameter: 2 mm; Gecko Optical, Perth, WA, Australia), which had a flaccid, thin-walled, infinitely compliant polyethylene bag (max. capacity: 1200 mL) tied onto and tightly wrapped around its distal end.[7,29] The catheter was connected via a three-way tap to a gastric barostat device (Distender Series II™, G & J Electronics Inc, Toronto, Ontario, Canada). The bag was positioned in the fundus of the stomach by inflating it with ~350 mL of air, and carefully pulling it back until its passage was restricted by the lower esophageal sphincter and then pushing it back in again by 2 cm.[7] The minimal distending pressure (MDP, defined as the intrabag pressure which first results in a bag volume of 30 mL air[31,32]) was then determined by gradually increasing intragastric pressure in 1-mmHg steps per minute. Intrabag pressure was then set at 2 mmHg above MDP and baseline intrabag volume was recorded for 10 min ($t = -10$ to 0 min), after which the participant received either STW5-II or placebo. Intrabag volumes were then recorded for 180 min ($t = 0$ to 180 min). The catheter was then removed, and the participant was offered a light lunch before leaving the laboratory.

2.4.3 | Part 3: Effects of STW5-II on antropyloroduodenal pressures

Eighteen participants completed this part (12M/6F, mean age: 27 ± 1 years, BMI: 22.3 ± 2.0 kg/m^2). Following arrival, a custom-built manometric catheter (outer diameter: 4 mm; Dentsleeve International, Mui Scientific, Mississauga, Ontario, Canada) was inserted through an anesthetized nostril and allowed to pass into the duodenum by peristalsis.[33] The manometric catheter consisted of 16 side holes, spaced at 1.5 cm intervals, with six side holes (channels 1–6) positioned in the antrum, a 4.5 cm sleeve sensor (channel 7), with 2 channels present on the back of the sleeve (channels 8 and 9), across the pylorus, and 7 channels in the duodenum (channels 10–16). The correct positioning of the catheter, so that the sleeve sensor straddled the pylorus, was maintained by continuous measurement of the transmucosal potential difference.[34] Once positioned, fasting motility was monitored continuously, and immediately after the end of phase III activity of the migrating motor complex, during a period of motor quiescence (phase I), recording of baseline motility commenced ($t = -10$ to 0 min). At $t = 0$ min, the participant received either STW5-II or placebo, and motility was recorded for 180 min ($t = 0$ to 180 min). At $t = 180$ min, the manometric assembly was removed, and the participant was offered a light lunch before leaving the laboratory.

2.5 | Measurements

2.5.1 | Esophago-gastric junction pressures

Eesophago-gastric junction pressures generated by the intrinsic lower esophageal sphincter and extrinsic crural diaphragm were digitized (20 Hz) and recorded with a computer-based system using commercially available software (MMS database software, version 9.3; Enschede, The Netherlands). The recordings were analyzed at baseline (i.e., $t = -15$ to -5 min) and in response to treatment ($t = 0$ to 120 min) using Swallow Gateway™ (Flinders University, South Australia, Australia). The esophago-gastric junction high-pressure zone was identified visually, and resting tone was assessed, that is, the pressures that were independent of esophageal peristalsis or other motor events, other than respiration. To analyze, a region of interest (ROI) "box" was selected over a duration of three respiratory cycles.[35] Consecutive ROIs were captured over the study period, at the mid-point of the baseline period (i.e., $t = -10$ min) and in 5-min intervals during $t = 0$ to 120 min. Within each ROI, the optimal esophago-gastric junction pressure domain was identified by a pressure band exceeding gastric pressure. The pressures within this domain were then analyzed to determine two metrics indicative of esophago-gastric junction resting tone: (1) the mean resting pressure (mmHg), defined as the mean maximum axial pressure above gastric pressure and (2) the esophago-gastric junction contractile integral (mmHg x cm) defined by the mean domain pressure (mmHg) above gastric pressure multiplied by the length of the domain (cm).[35] Transient lower esophageal sphincter relaxations (TLESRs), defined by LESR of >10 s duration, initiated without a swallow occurring within 4 s before, or 2 s after, relaxation onset and typically associated with an impedance detectible reflux episode (gas, mixed, or liquid), were also assessed.[36]

2.5.2 | Proximal gastric volume

Proximal gastric tone was quantified by changes in intragastric volume at a given pressure. Intrabag volumes and pressures were

digitized and recorded on a computer-based system running commercially available software (Protocol Plus™, G & J Electronics, Toronto, Ontario, Canada). Intrabag volumes were expressed as means of 10-min segments for baseline (i.e., $t = -10$ to 0 min) and in response to treatment ($t = 0$ to 180 min). Absolute maximum volume following treatment (i.e., between $t = 0$ and 180 min) was also determined.

2.5.3 | Antropyloroduodenal pressures

Antropyloroduodenal pressures were digitized and recorded with a computer-based system running commercially available software (MMS database software, version 8.17; Solar GI, Enschede, The Netherlands). Data were analyzed during baseline ($t = -10$ to 0 min) and subsequent 15-min intervals from 0 to 180 min, for the absolute number, and mean amplitude, of antral, duodenal, and isolated pyloric pressure waves (IPPWs), as well as mean basal pyloric pressure, using custom-written software modified to our requirements (A. Smout, University Medical Centre, Amsterdam, Netherlands). Antral and phasic pyloric pressure waves were defined by an amplitude of ≥10 mmHg with a minimum interval of 10 s between peaks. Duodenal pressure waves were defined by an amplitude of ≥10 mmHg, with a minimum interval of 3 s between peaks.[37] Basal pyloric pressure was calculated by subtracting the mean basal pressure recorded at the most distal antral channel from the mean basal pressure recorded at sleeve.[37] The total numbers and mean amplitudes of antral and duodenal pressure waves were used to calculate antral and duodenal motility indices (MIs) using the following equation[38]:

$$\text{MI} = \text{natural logarithm}\left[\left(\text{number of waves} \times \sum \text{amplitude}\right) + 1\right].$$

2.6 | Statistical analysis

The number of participants in each study part was determined by power calculations based on our previous work.[29] We calculated that $n = 16$ participants would allow the detection of a difference of 46 mL in intragastric volume and $n = 18$ a difference of 93 mmHg in antral motility index, between STW5-II and placebo, with a power of 80% and $\alpha = 0.05$. As no data were available for esophago-gastric junction pressures, power calculations could not be performed, thus, $n = 16$ participants were included.

To evaluate the effects of treatment over the study period, data were analyzed in three 60-min segments, that is, between 0–60 min, 60–120 min, and 120–180 min, except in study part 1, which, for logistical reasons, only included $t = 0$–60 min and 60–120 min. Esophago-gastric junction resting pressures and esophago-gastric junction contractile integral (part 1), intrabag volumes (part 2), number and amplitude of antral, duodenal and pyloric pressure waves, basal pyloric pressure, and antral and duodenal MIs (part 3) were analyzed using mixed effects models, with treatment, time, and their interaction as fixed factors, and baseline data as a covariate. A first-order auto-regressive covariance structure was used to account for repeated time points and visits per participant. Post-hoc comparisons, adjusted for multiple comparisons using Bonferroni's correction, were performed where mixed model analyses revealed significant effects. The number of post-meal TLESRs during 0–60 min and 60–120 min (part 1), maximum intrabag volume and MDP (part 2), and baseline values for all parameters (parts 1–3) were analyzed by paired samples *t*-test. Statistical analysis was performed in collaboration with a biostatistician, using SPSS software (version 28.0; IBM Corp, Armonk, NY, USA). Differences were considered statistically significant at $p \leq 0.05$. All data are expressed as means ± SEM.

3 | RESULTS

All participants completed all study visits without any adverse events.

3.1 | Part 1: Effects on esophago-gastric junction pressures

3.1.1 | Esophago-gastric junction pressures

There were no differences in baseline esophago-gastric junction resting pressure ($p = 0.526$) or esophago-gastric junction contractile integral ($p = 0.394$) between study days, or any effects of treatment (resting pressure, $t = 0$–60 min: $p = 0.777$, $t = 60$–120 min: $p = 0.832$; contractile integral, $t = 0$–60 min: $p = 0.969$, $t = 60$–120 min: $p = 0.802$). On both study days, both resting pressure and contractile integral decreased slightly after the meal before gradually returning to baseline again (Figure 2A,B).

3.1.2 | TLESRs

There was no effect of treatment on number of TLESRs ($t = 0$–60 min: $p = 0.564$, $t = 60$–120 min: $p = 0.464$; Figure 2C).

3.2 | Part 2: Effects on proximal gastric volumes

3.2.1 | Intrabag volumes

There were no differences in MDP (mmHg; STW5-II: 8.0 ± 0.6, placebo: 8.0 ± 0.6; $p = 0.164$) or baseline intrabag volumes at MDP + 2 between study days (mL; STW5-II: 161 ± 15, placebo: 178 ± 17; $p = 0.305$). There were effects of treatment on maximum intrabag volume (mL; STW5-II: 340 ± 38, placebo: 251 ± 30; $p = 0.007$) and intrabag volume at $t = 120$–180 min ($p = 0.011$), but no significant effects at $t = 0$–60 min ($p = 0.170$) or $t = 60$–120 min ($p = 0.145$) (Figure 3).

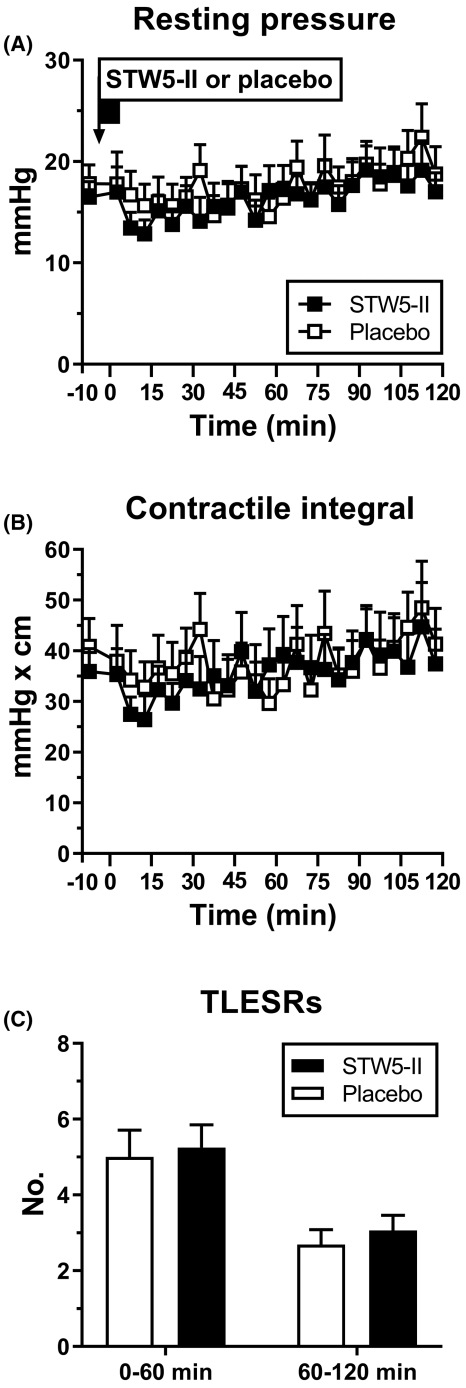

FIGURE 2 Esophago-gastric junction (EGJ) resting pressure (A) and contractile integral (B) and transient lower esophageal sphincter relaxations (TLESRs) (C) in response to STW5-II or placebo ($t=0$–120 min) administered prior to ingestion of a 100 g minced beef burger (270 kcal, 25 g protein, 21 g fat) and 150 mL dextrose solution (10%, 62 kcal). Black box marks the duration of test meal ingestion ($t=-5$ to 0 min). Data were analyzed in 60-min segments ($t=0$–60 min, $t=60$–120 min) using mixed effects models, with treatment, time, and their interaction as fixed factors and baseline data as a covariate. There was no effect of treatment on resting pressure or contractile integral. Data are means ± SEM; $n=16$.

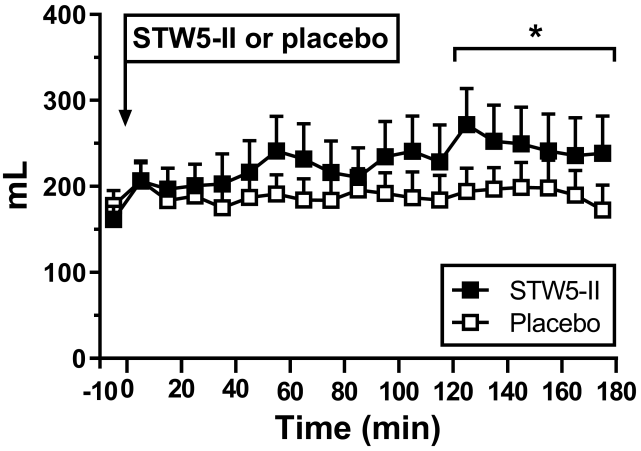

FIGURE 3 Intrabag volumes in response to STW5-II or placebo ($t=0$–180 min). Data were analyzed in 60-min segments ($t=0$–60 min, 60–120 min, and 120–180 min) using mixed effects models, with treatment, time, and their interaction as fixed factors and baseline data as a covariate. There was an effect of STW5-II on intrabag volume at $t=120$–180 min (*$p=0.011$), compared with placebo, but not at $t=0$–60 min or $t=60$–20 min. Data are means ± SEM; $n=16$.

3.3 | Part 3: Effects on antropyloroduodenal pressures

3.3.1 | Antral pressures

There were no differences in baseline number ($p=0.394$), amplitude ($p=0.350$), or MI ($p=0.426$) of antral pressure waves between study days. There was an effect of treatment on the number of antral pressure waves ($p=0.040$) and the antral MI ($p=0.032$), but not the amplitude ($p=0.441$), at $t=60$–120 min, which were both greater following STW5-II compared with placebo. There were no effects on the number, amplitude, or MI of antral pressure waves between $t=0$–60 min (number: $p=0.207$; amplitude: $p=0.418$; MI: $p=0.115$) or $t=120$–180 min (number: $p=0.593$; amplitude: $p=0.779$; MI: $p=0.989$) (Figure 4A–C).

3.3.2 | Pyloric pressures

There were no differences in baseline number ($p=0.698$) or amplitude ($p=0.331$) of IPPWs, or basal pyloric pressure ($p=0.568$), between study days, and no effects of treatment ($t=0$–60 min, number: $p=0.333$; amplitude: $p=0.369$; basal pyloric pressure: $p=0.292$; $t=60$–120 min, number: $p=0.705$; amplitude: $p=0.123$; basal pyloric pressure: $p=0.713$; $t=120$–180 min number, $p=0.481$; amplitude: $p=0.976$; basal pyloric pressure: $p=0.661$) (Figure 5A–C).

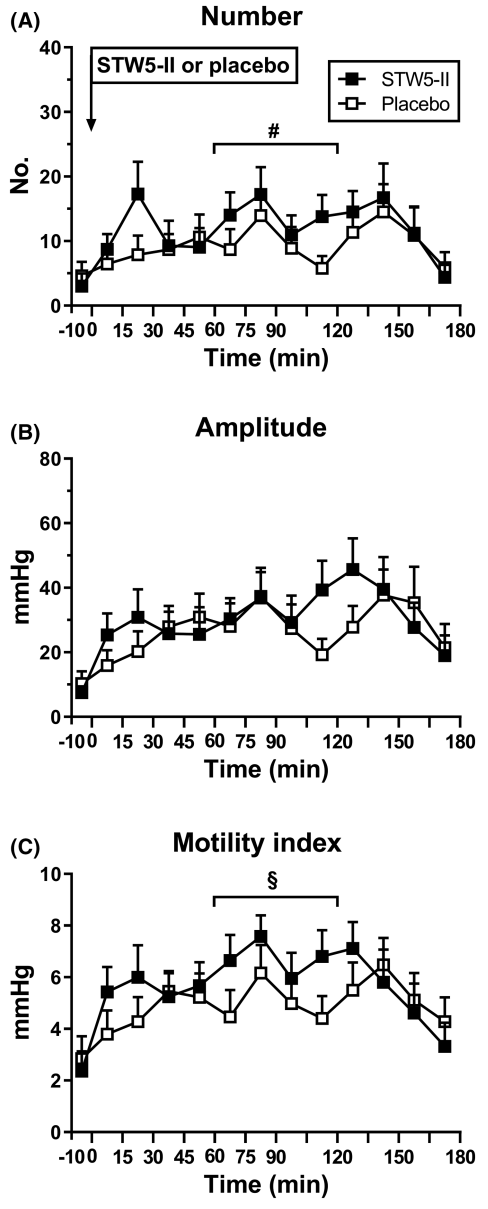

FIGURE 4 Number (A), amplitude (B), and (C) motility index (MI) of antral pressure waves in response to STW5-II or placebo ($t = 0–180$ min). Data were analyzed in 60-min segments ($t = 0–60$ min, 60–120 min, and 120–180 min) using mixed effects models, with treatment, time, and their interaction as fixed factors and baseline data as a covariate. There was an effect of treatment on the number of antral pressure waves (#$p = 0.040$) and antral MI (§$p = 0.032$) at $t = 60–20$ min, both of which were greater following STW5-II compared with placebo. There were no effects on the number, amplitude, or MI of antral pressure waves between $t = 0–60$ min or $t = 120–180$ min. Data are means ± SEM; $n = 18$.

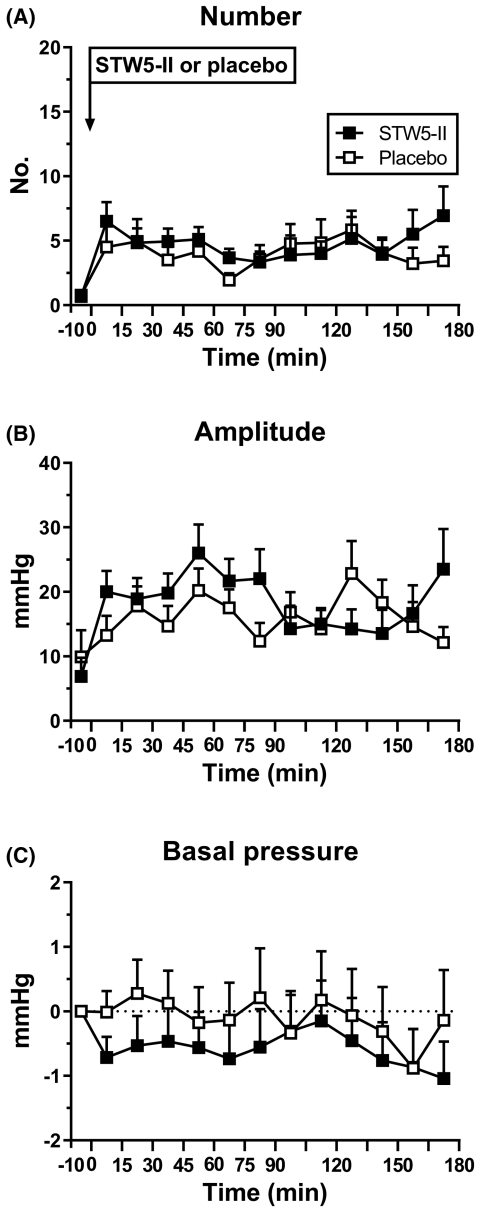

FIGURE 5 Number (A) and amplitude (B) of isolated pyloric pressure waves (IPPWs), and basal pyloric pressure (C) in response to STW5-II or placebo ($t = 0–180$ min). Data were analyzed in 60-min segments ($t = 0–60$ min, 60–120 min, and 120–180 min) using mixed effects models, with treatment, time, and their interaction as fixed factors and baseline data as a covariate. There were no effects on the number or amplitude of IPPWs or basal pyloric pressure. Data are means ± SEM, $n = 18$.

3.3.3 | Duodenal pressures

There were no differences in baseline number ($p = 0.235$), amplitude ($p = 0.940$), or MI ($p = 0.971$) of duodenal pressure waves between study days, and no effects of treatment ($t = 0–60$ min, number: $p = 0.427$; amplitude: $p = 0.601$; MI: $p = 0.595$; $t = 60–120$ min, number: $p = 0.561$; amplitude: $p = 0.343$; MI: $p = 0.688$; $t = 120–180$ min number, $p = 0.306$; amplitude: $p = 0.548$; MI: $p = 0.637$; Figure 6A–C).

4 | DISCUSSION

Our study has characterized the effects of STW5-II on upper GI motor functions in healthy participants. We established that STW5-II reduces proximal gastric tone, as measured by the increase

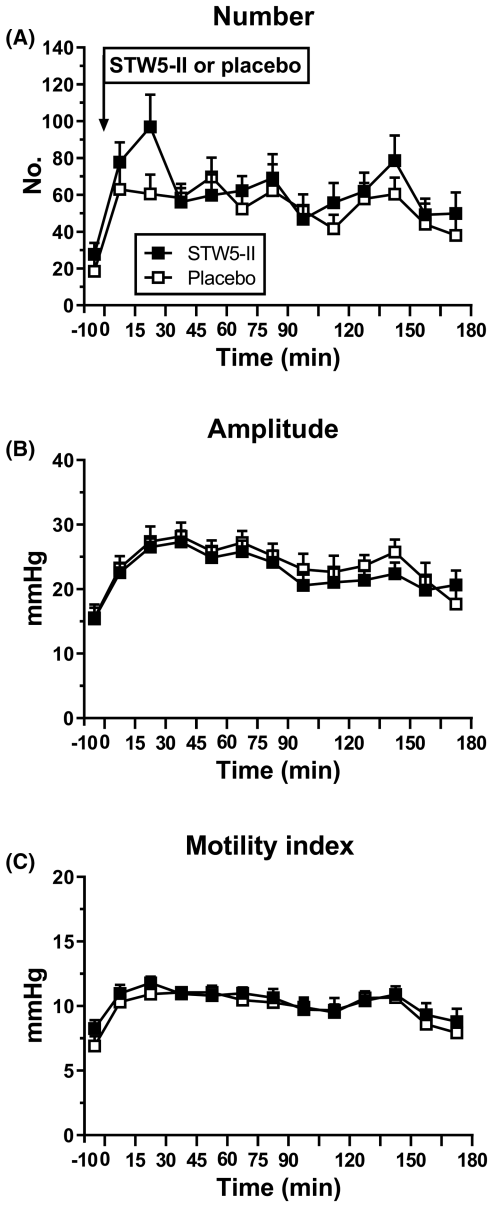

FIGURE 6 Number (A), amplitude (B), and (C) motility index (MI) of duodenal pressure waves in response to STW5-II or placebo ($t = 0–180$ min). Data were analyzed in 60-min segments ($t = 0–60$ min, 60–120 min, and 120–180 min) using mixed effects models, with treatment, time, and their interaction as fixed factors and baseline data as a covariate. There were no effects on number, amplitude, or MI of duodenal pressure waves. Data are means ± SEM; $n = 18$.

in volume in the intragastric bag at constant pressure, and stimulates antral pressure. In contrast, it had no effects on esophago-gastric junction, pyloric, or duodenal pressures.

In subgroups of patients with disorders of gut–brain interaction, GI symptoms are associated with disordered upper GI motility, including lower esophageal sphincter dysfunction (leading to reflux), impaired proximal gastric tone, and relaxation and altered gastric emptying and intragastric meal distribution. A subgroup of patients with functional dyspepsia exhibits hypersensitivity to gastric distension,[1] many experience symptoms even after small amounts of food,[39] and the experience of early satiety is associated with impaired proximal gastric relaxation.[9] Treatment options for these disorders remain limited and less than optimal. Not surprisingly, there has been a longstanding interest in the use of herbal remedies in an attempt to alleviate digestive symptoms. Indeed, preparations containing herbal extracts, such as peppermint oil or menthol, or combinations of herbs, such as STW5 and STW5-II, have been demonstrated to be at least as effective as pharmaceutical drugs in improving GI symptoms, including epigastric pain, postprandial fullness, and early satiation.[18,24] There is, however, a lack of information in relation to the mechanisms underlying these effects.

4.1 | Effects on proximal gastric tone

Both STW5 and STW5-II reduce tone in muscle strips of guinea pig fundus,[25–27] and STW5 reduces proximal gastric tone, as measured with a gastric barostat, in healthy humans.[29] The current study establishes that STW5-II also reduces proximal gastric tone in healthy humans. This effect was statistically significant in the third hour after STW5-II administration, but it should be recognized that intrabag volumes increased continually over time, and mean volumes were greater than after placebo throughout the study period. The magnitude of effect is substantial—comparable with that of a duodenal nutrient infusion.[40] In view of these observations, the relationship between symptom improvement by STW5-II with the magnitude of changes in gastric tone, as well as the effect of STW5-II on the sensitivity to gastric distension, warrants evaluation in individuals with functional dyspepsia.

4.2 | Effects on antropyloroduodenal contractility

STW5-II also increased antral contractility, in line with our finding for STW5.[29] A subgroup of patients with functional dyspepsia has been described to have a "wide antrum,"[10] suggesting exaggerated redistribution of food to the distal stomach, and in healthy young and older participants, antral filling was correlated with the perception of fullness.[41,42] Thus, the potential effect of STW5-II on intragastric meal distribution warrants evaluation. In our previous study, STW5 did not have a clinically meaningful effect on gastric emptying (we found only a very minor effect on liquid emptying). In the current study, we did not evaluate the effects of STW5-II on gastric emptying, however, that it reduced proximal gastric tone, while increasing antral contractility, without affecting pyloric or duodenal pressures, suggests that it is unlikely to have a major effect.

4.3 | Effects on esophago-gastric junction pressures

There is some, although limited, evidence from preclinical studies that STW5 may be protective against reflux esophagitis. For

example, in an acute model of reflux esophagitis in rats, STW5, when administered for 5 days prior to experimentally inducing reflux esophagitis, reduced the severity of esophageal ulcerative lesions,[43] an effect that was independent of esophageal pH. In a preliminary report from an in vitro study on guinea pig tissue, STW5 also increased the tone of the lower esophageal sphincter smooth muscle.[28] Whether STW5, or STW5-II, affects lower esophageal sphincter pressure in humans has not been evaluated. In the current study, we determined the esophago-gastric junction contractile integral, which provides a global assessment of antireflux barrier function, taking into account mean resting pressure, maximum esophago-gastric junction pressure over time, and axial pressure during inspiration, and found no effect of STW5-II. While the lower esophageal sphincter alone represents only one component of the anatomically complex esophago-gastric junction barrier mechanism, our data nevertheless suggest that the protective effect against esophageal lesions, observed in preclinical studies, may not be a result of reduced reflux, due to improved resting esophago-gastric junction barrier function and/or attenuated TLESR-related reflux triggering, but perhaps, due to the anti-inflammatory, or antiulcerogenic, properties of STW5-II.[44]

4.4 | Study limitations

The limitations of our study should be appreciated. The studies were performed on healthy participants. We characterized effects on proximal gastric tone and antropyloroduodenal pressures in the fasting state and postprandial effects warrant evaluation. The observed effects on proximal gastric tone and antral contractility suggest that intragastric meal distribution will be modified, which may be beneficial in the subgroup of patients with functional dyspepsia in whom intragastric distribution is abnormal.[6]

5 | CONCLUSIONS

In conclusion, in healthy individuals, acute administration of STW5-II reduces proximal gastric tone and stimulates antral motility but does not modulate esophago-gastric junction, pyloric, or duodenal pressures. Studies to evaluate the relationship between these gastric motor effects and symptom relief in patients with functional dyspepsia are warranted.

AUTHOR CONTRIBUTIONS

PCEF was involved in the study design and responsible for coordination and performance of the studies, subject recruitment, data and statistical analysis, and drafting of the manuscript. VB was involved in the performance of studies and data analysis. TO was involved in the study design, performance of studies, data analysis and interpretation, and drafting of the manuscript and provided technical assistance. CC was involved in the performance of studies and data interpretation. KLJ was involved in the study design, data analysis, and drafting of the manuscript. MH was involved in data interpretation and drafting of the manuscript. CFB was responsible for the study concept and design, data and statistical analysis, data interpretation, and drafting of the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

CFB has received consultancy fees from Steigerwald GmbH. KLJ is a shareholder of Glyscend. MH has participated in advisory boards and/or symposia for Sanofi, Eli Lilly, and Inova and has received honoraria for this activity. He is a shareholder with Satiogen and Glyscend. PCEF, VB, TO, and CC have no conflict of interest to declare. The sponsor did not influence data collection, analysis, or interpretation, and the authors had full control over the data.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CLINICAL TRIAL REGISTRY NUMBER

The study was registered as a clinical trial with the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au; registration IDs: ACTRN126221000480886, ACTRN12621000149864, ACTRN12621000116820).

ORCID

Taher Omari https://orcid.org/0000-0001-5108-7378
Christine Feinle-Bisset https://orcid.org/0000-0001-6848-0125

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