Evaluation of the impact of the HLNatural, Inc. Upset Stomach Relief product on the reduction of symptoms in adults who suffer from mild to moderate indigestion and heartburn

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Sponsored by:
HLNatural, Inc.

Principal Investigator:
Soyona Rafatjah, MD

Version Number
Version 1.1

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July, 17th 2019

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- *U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)*
- *ICH GCP E6*
- *Completion of Human Subjects Protection Training*
- *NIH Clinical Terms of Award*

Refer to:
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/45-cfr-46/index.html
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____
Name

Project Manager:

Signed: _____ Date: _____
Name

Sponsor:

Signed: _____ Date: _____
Name

Statistician

Signed: _____ Date: _____
Name

Title: Evaluation of the impact of the HLNatural, Inc. Upset Stomach Relief product on the reduction of symptoms in adults who suffer from mild to moderate indigestion and heartburn

Population: The study will consist of at least 200 participants who self-identify as satisfying the inclusion criteria. The geography of participant enrollment will be spread across the United States.

Number of Sites: This is a single (virtual) site study.

Study Type **Single site, prospective, one arm observational study of Minimal Risk.**

Study Duration: The duration of the study is expected to be 6 months depending on the speed of enrollment.

Participant Duration: The duration of participation for each participant is expected to be 60 days.

Objectives: The purpose of this study is to demonstrate whether this plant-based remedy will reduce the severity of symptoms of occasional indigestion and heartburn. This trial will gather data on performance of the test product. These data will be used to describe the performance currently, and potentially to design a two-arm trial in the future

Primary Endpoints:

- The primary endpoint is reduction in indigestion severity and reduction in heartburn severity. There is no control group for the primary analysis.

Secondary Endpoints:

- The time to other intervention will be analyzed.
- A longitudinal analysis will be performed for participants who report on more than one incident of heartburn or indigestion.
- Adverse events will be summarized.
- An additional data presentation will consist of results from both Treatment and Control in similar studies appearing in the literature. There will be no formal statistical comparison of results from this study and historical studies.
- The Net Promoter Score will be summarized and compared against outcomes.
- Comparison against normal behavior will use the paired sample t-test

Table OF Contents

1. KEY ROLES

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2. Background Information and Scientific Rationale

2.1. Background Information

The primary hypothesis of the present study is that supplementation with the Upset Stomach Relief test product will reduce the severity of the symptoms of occasional indigestion and heartburn.

Dyspepsia, also known as indigestion, is a common symptom with an extensive differential diagnosis and a heterogeneous pathophysiology. It occurs in approximately 25 percent of the population each year, but most affected people do not seek medical care. Approximately 25 percent of patients with dyspepsia have an underlying organic cause. However, up to 75 percent of patients have functional (idiopathic or non-ulcer) dyspepsia with no underlying cause on diagnostic evaluation. Patients with functional dyspepsia usually describe postprandial fullness, early satiety, and/or epigastric pain/burning. Symptoms may be severe enough to limit usual activities. Some patients may have nausea, vomiting, or heartburn; however, these symptoms are usually infrequent. [28] The most common approach to treat occasional indigestion and heartburn is to use antacids to neutralize what is often believed to be an overproduction of stomach acid. This acid-blocking approach can perpetuate the problem when used over a long period of time. Acid blocking also has the drawback of causing deficiencies in certain vitamins and minerals over time, such as calcium. By interfering with the digestive process, an overgrowth of bacteria and imbalances in gut health can also worsen health states. The Upset Stomach Relief test product is an herbal solution with ingredients that may ease occasional indigestion and heartburn, while helping to strengthen the digestive tract over time. [4]

There are several causes of indigestion. Acid accumulation and improper gastrointestinal emptying can both prompt dyspepsia. Additionally, stomach or intestinal ulcers formed by bacteria named *Helicobacter pylori* can result in infection that ultimately will cause indigestion. Other potential causes can be from the intake of over-the-counter medications, like ibuprofen, overeating, fatty, greasy, or spicy food, alcohol, and caffeine. [5]

While dietary and lifestyle changes can ease the symptoms of indigestion and heartburn, HLNatural, Inc. created the test product to reduce occasional indigestion and heartburn. The test product is a plant-based remedy formulated with ingredients that have demonstrated

efficacy reducing symptoms associated with occasional indigestion and heartburn. The product combines ingredients into an easy to consume capsule designed to be consumed at the onset of symptoms or before each meal, up to three times per day. The test product is 1) DGL Extract, 2) Artichoke Leaf Extract, 3) Ginger Root Extract (6% gingerols), 4) Chamomile (1% Apigenin), 5) Marshmallow Root Extract, 6) Capsule (Hydroxypropyl Methyl Cellulose, Purified Water, Carrageenan, Potassium Chloride), , 7) Rice Hull Concentrate. Below, the 7 ingredients of the test product are listed. All ingredients are Generally Recognized as Safe (GRAS) by the FDA.

Upset Stomach Relief

Active Ingredients: Licorice Extract, Artichoke Leaf Extract, Chamomile, Marshmallow Root, Ginger.

Inactive Ingredients:Capsule (Hydroxypropyl Methyl Cellulose, Purified Water, Carrageenan, Potassium Chloride), Rice Hull Concentrate.

The ingredients in the test product have been included because they have demonstrated benefit for digestive health. The justifications for their inclusion are briefly described here:

Licorice has a long history of traditional use in promoting digestive health. DGL is a type of extract of licorice in which the glycyrrhizin has been removed, which helps prevent side effects that can occur in some people from regular Licorice use. Scientific investigation into the mechanism of activity of DGL for providing digestive support shows that it helps in maintaining digestive comfort by maintaining the integrity of the protective mucosal lining in the stomach and intestine. It is also an anti-spasmolytic, which helps to relax the intestinal wall and aid in digestive comfort. [10, 16, 17, 18]

Artichoke Leaf Extract helps stimulate and aid the digestive process. Artichoke Leaf extract is a traditional herbal digestive bitter known to stimulate the digestive process. Artichoke Leaf extract has been shown in studies to relieve occasional heartburn. [9]

Marshmallow Root has a long history of traditional use for soothing mucosal membranes. The mucilage-rich roots of Marshmallow are thought to be responsible for many of the pharmacological activities of Marshmallow. Preclinical research shows that the mucilaginous nature can help form a protective coating on the mucosal lining, which acts as a shield from irritants and exerting spasmolytic and antisecretory properties. [11, 19, 20, 21, 22]

Ginger is a spice that has long history of traditional use for digestive discomfort. Clinical research shows that Ginger supports health through its benefits to the immune, respiratory

systems, aiding digestion, and promoting normal cytokine balance. Ginger works on the gut-brain axis by supporting neurotransmission which supports gastric emptying, upper GI digestive comfort and intestinal motility. It exerts a gastroprotective effect and relief of occasional heartburn. [7, 8, 23, 24]

Chamomile is one of the most world-renowned herbs for promoting healthy digestion. It contains a phytochemical called apigenin which has a number of health-promoting benefits, including promoting healthy cytokine balance. Chamomile is also antispasmodic, affecting the muscles of the intestine and promoting digestive comfort. Additionally, stress and mood have been proven to affect indigestion and in clinical studies, Chamomile has shown support for relaxation and healthy mood. [3, 6, 25, 26, 27]

2.2. Scientific Rationale

The test product's formulation is based on the most promising clinical research on natural ingredients that safely impact digestive health and relieve symptoms of occasional indigestion and heartburn. While the evidence to support the use of these individual active ingredients is growing, well-designed human clinical trials showing benefit are necessary to demonstrate efficacy of the test product's unique formulation.

The present study will include a minimum of 200 participants who suffer from the symptoms of mild to moderate indigestion and/or heartburn and is designed to observe the level of symptom reduction in this population after consuming the test product.

2.2.1. Potential Risk

Minimal risk is foreseen for participants through their participation in the study. All the ingredients composing the test product are Generally Recognized as Safe (GRAS) by the FDA for daily consumption at their present concentrations.

The ingredients in the test product have been shown to have some theoretical drug interactions which have been listed in the appendix. (*Appendix A*)

Potential side-effects have been observed in high doses which are significantly greater than the dose of the capsules as recommended in the instructions for use:

- Headache
- Amenorrhea
- Upset Stomach
- Diarrhea
- Hives
- Difficulty breathing
- Facial swelling

- Drowsiness
- Tiredness
- Vomiting

This study is determined by Sponsor and Principal Investigator to be a Minimal Risk Study.

Minimal risk is defined by 45 U.S. Code of Federal Regulations (CFR) 46.102 (i) as follows:

"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102

2.2.2. Known Potential Benefits

Over-the-counter and prescription remedies for occasional indigestion and heartburn have known undesirable side effects. Additionally, these products often contain additives, dyes, fillers and other unnatural or synthetic ingredients that consumers are looking to avoid. As such, these consumers are seeking natural, plant-based alternatives for symptom relief. Research participants may benefit from the intervention by eliminating such unwanted side effects when treating their symptoms of occasional indigestion and heartburn while achieving symptom relief. If the intervention is shown to be efficacious, this would provide a viable solution for those people who want to decrease their use of drugs that contain undesired ingredients. Other benefits include detailed surveillance of symptoms and documentation of activities, routine medications and supplements that may provide participant and their regular physician or other healthcare provider with useful information for diagnosis and treatment of symptoms should they occur.

2.2.3. Minimization of Risks

Research participants will be carefully screened to meet enrollment criteria. Participants meeting exclusion criteria will not be enrolled. The study participant informed consent will be presented with clear description of the study requirements and opportunity to have questions answered before enrollment. Once an event occurs, review of symptoms will be ascertained at onset, 15, 30, and 60 minutes. Reporting of adverse events will be reviewed routinely and in accordance with regulatory guidelines (21CFR, GCP) by the Principal Investigator. Participants with occurrence of worsening symptoms or adverse

events will be advised to stop taking the test product, may seek medical attention, and exit the study.

3. Study Objectives

The purpose of the present study is to evaluate 1) the impact of the test product on symptoms of occasional indigestion and heartburn in 200 adult participants who suffer from occasional indigestion and heartburn and 2) the subjective experience of these participants related to general health, indigestion and heartburn symptoms, and personal experience with the test product.

This will be evaluated based on the primary and secondary endpoints. These endpoints, the analysis populations, and their respective measures are described below. Further details on the methods for measuring the outcomes can be found in the Study Outcome Measures and Analysis Plan sections.

Primary Endpoint:

The primary endpoint has two components, reduction in indigestion severity and reduction in heartburn severity. Participants will be asked to rate each symptom (bloating, early fullness during a meal, pain or discomfort in the upper abdomen, burning in the upper abdomen, pain/burning in the center of your chest, nausea, vomiting, and burping) on a 4-point scale at 4 time points: prior to taking the test product, 15, 30 , and 60 minutes after taking the test product. The improvement in symptoms from baseline will be evaluated on a pairwise basis separately for each component and each time point. P-values will be computed for the improvement. Given that indigestion can impact an individual's quality of life, the primary endpoint was chosen to see the test product's effects on symptoms. [1, 9, 12]

Secondary Endpoint:

Secondary endpoints will be analyzed to evaluate safety and patient satisfaction with relief of symptoms. These include:

- The time to other intervention will be analyzed.
- A longitudinal analysis will be performed for participants who report on more than one incident of heartburn or indigestion.
- Adverse events will be summarized.
- An additional data presentation will consist of results from both Treatment and Control in similar studies appearing in the literature. There will be no formal statistical comparison of results from this study and historical studies.
- The Net Promoter Score will be summarized and compared against outcomes.
- Comparison against normal behavior will use the paired sample t-test.

4. Study Design

The present study will be a single site, prospective, one arm observational study of minimal risk consisting of at least 200 participants who suffer from symptoms of occasional indigestion and heartburn. The participants must meet additional inclusion/exclusion criteria (see Inclusion/Exclusion Criteria). Participants will begin taking the capsules at the onset of indigestion and heartburn symptoms. Onset is defined as the point in time the participant takes the test product for relief of symptoms. When the participant decides to take the test product, they will report and rate their symptoms on a 4-point Likert scale in the symptom diary prior to taking the test product. After consuming the test product, the participant will complete a 4-point Likert scale for each symptom at 15 minutes, 30 minutes, and 1 hour after taking the test product. If needed the participant will be allowed to take an alternative medication an hour after taking the test product. If medication is taken, the participant will record this in their symptom diary.

Study enrollment and management will be decentralized, where participants do not visit an investigator or a clinic for clinical assessment. The participants will participate in the study at home. All data collected from during this study will be reported by the participant via eCRFs, eDiary, and other electronic data entries. If a visit is required, it will be conducted via remote contact by telephone.

4.1. Test Product

Below is the description of the test product and its ingredients.

Upset Stomach Relief Product

Description: Combining Deglycyrrhizinated licorice (DGL), Artichoke Leaf, Marshmallow Root, Ginger, and Chamomile for comprehensive, yet gentle plant-based support for occasional indigestion and heartburn relief. This formula is designed to promote digestion and feelings of digestive comfort.

Active Ingredients: Licorice Extract, Artichoke Leaf Extract, Chamomile, Marshmallow Root, Ginger.

Inactive Ingredients:Capsule (Hydroxypropyl Methyl Cellulose, Purified Water, Carrageenan, Potassium Chloride), Rice Hull Concentrate.

4.2. Required Behavior

During the hour directly following consumption of the test product, no medication or supplementation (including all CBD products) other than the test product should be taken

for relief of indigestion and heartburn symptoms. Once the 1-hour report has been recorded the participant may take other medications or supplements. If medication is taken, the participant will record this in their symptom diary.

Participants are asked to limit the consumption of alcohol beverages to less than or equal to two drinks per day.

4.3. Participation Period

Participants are expected to participate in the study for 60 days after study start. The product may be used after each onset of indigestion and heartburn episode, but not exceeding three times per day. Participants will be discontinued from the study 60 days after Study Start or after three recorded episodes of indigestion and heartburn. Study start is defined as the day the participant recorded received receipt of the test product on the start form in the platform.

4.4. Data Collection

All data in the present study will be self-reported by the participant and collected via their online portal (Hawthorne Effect Study Visit Management System (HE VMS)). Participants will be asked to take the test product according to the instructions for use, complete study surveys and respond to study reminders during the course of the study. The instructions for use and study forms can be found in the appendix. (*Appendices B, D, E, F, G*)

5. Study Population

5.1. Selection of the Study Population

The study population will consist of at least 200 participants who suffer from symptoms of indigestion and heartburn. The participants will otherwise be in good health.

The target sample size for this study is initially 200 participants, with a desired sample of 97 treated participants. This is described in detail in the Statistical Considerations section.

At such time as 180 participants have been enrolled, the available data will be analyzed using a constant hazard model to determine if it seems realistic that the desired number of 97 treated participants will be met by the end of follow-up. If the expected number of treated participants is less than 97, the target sample size will be increased as needed, considering both the desire for 97treated participants and the timelines of the trial sponsor. The actual outcomes of treated

participants will not be considered in this analysis, merely whether or not enrolled participants have reported starting using the test product.

Enrollment will be stopped once the target number of participants has been enrolled, no further participants will be offered a place in the trial once the target sample size criteria has been met. All participants who have already been offered places, but who have not yet consented, will be allowed to participate as long as they have signed the study consent within 15 days and the total number of participants does not exceed 125% of the target (either 200 or the recomputed target if recomputation has been performed.)

In order to ensure an age and sex distribution that is reasonably representative of the US population, enrollment may be stopped early in some age and sex groups.

Target population for this study are candidates who suffer from symptoms of occasional indigestion and heartburn.

Participants will be enrolled from across the United States. No participants will be enrolled outside of the United States. It is expected that the geographical distribution of the participants enrolled in the study will correlate with the geographical distribution of the general population across the United States.

Participants will be recruited via digital advertisements and social media.

After clicking on an advertisement, potential participants will then be directed to a website where they will complete a screening questionnaire (See *Appendix C*). The screening questionnaire will automatically qualify or disqualify them for study participation. If the participant qualifies, they will be provided an informed consent. Upon completion of the informed consent they will be deemed enrolled in the study.

5.2. Inclusion/Exclusion Criteria

Prior to being enrolled, participants will fill out a screening questionnaire. The screening questionnaire will automatically qualify or disqualify them for study participation. The full screening questionnaire can be found in the Appendix (*Appendix C*). If the participant qualifies, they will be provided an informed consent. Upon completion of the informed consent they will be deemed enrolled in the study.

Inclusion Criteria:

Adult candidates who are in overall good health but who suffer from the symptoms of indigestion.

Participants will be deemed to be in good health if they do not report any of the existing medical conditions asked about in the screening questionnaire.

Exclusion Criteria:

- Age <18 years old.
- Unwilling to take test product for their symptoms.
- Are able to swallow pills.
- Allergy to any of the following: Licorice, Artichoke Leaf, Marshmallow Root, Ginger, Chamomile, Cellulose Capsule, Rice Hull Concentrate, Carrageenan.
- Participants who have been prescribed any medication by their physician for any GI disorder or medication that can affect the GI system.
- Participants with previous diagnosis of cancer or with previous surgery of the upper gastrointestinal tract or of the biliopancreatic system (except for cholecystectomy)
- Pregnant women or breastfeeding.
- Alcohol consumption more than 10 drinks per week
- Participants who are currently using anticoagulation medications daily. (Aspirin, Coumadin, Heparin etc.)

6. Study Evaluation

6.1. Study Procedures

- Candidates will review information about the study and complete a screening form.
- During the screening process, the candidate will be asked questions regarding their symptoms and medical history to ensure that they meet the requirements to participate in this study. Potential participants will also be asked questions to ensure that they do not meet any of the exclusion criteria and meet all of the inclusion criteria.
- After successful screening (participant does not meet any exclusion criteria), participants will review and sign study informed consent form.
- Upon verification of signed informed consent, participant will be enrolled into the study.
- At time of enrollment, participant will be given access to the HIPAA compliant study portal.
    - The study portal provides access to study information, signed informed consent form, instructions for test product use, frequently asked questions, study surveys, symptom diary, and data collection tools.
- Participant shall complete baseline assessments upon access to the portal.
    - Baseline assessment will include questions regarding the participants' demographics, medications, detailed information regarding their indigestion/heartburn including treatment.
- To ensure that baseline assessments are completed before test product is used by the participant, study materials and study welcome package will be shipped to the participant once the clinical study manager/clinical ops coordinator confirms that the baseline assessment has been completed.
- The welcome package will include an information sheet that will outline instructions for their participation in the trial, the test product, and paper forms of the documents (paper form of

study documents will be provided for real time data collection, in the event that the participant cannot log into the study portal to input data).

- Once the participant receives the test product, the participant will log into the study portal to acknowledge the receipt of the test product.
- Study start date will be the reported date of receipt of test product.
- Participant will be sent weekly email reminders that remind them of their participation in the study.
- At the onset of the indigestion and heartburn episode, the participant will start a Symptom Diary and complete a 4-point Likert scale for each of the symptoms they are experiencing.
    - Onset is defined as the point in time the participant takes the test product for relief of symptoms.
- After completing the surveys, the participant will take the test product. The participant will take 2 capsules per indigestion and heartburn episode. With a max of 6 capsules per day. (If participant takes 6 capsules in 1 day this will be defined as 3 indigestion and heartburn episodes and the participant will be exited from the study).
- After taking the test product, the participant will complete a 4-point Likert scale assessment for each symptom at 15 minutes, 30 minutes, and 1 hour after taking the test product.
- When the participants symptoms have resolved , the participant will complete the symptom diary.
- If the participant takes any other medication outside of the test product, the participant will record this on the symptom diary.
    - The participant is allowed to take alternative medications or supplements AFTER 1 hour from taking the test product.
- After taking the test product, the participant will be instructed to fill out an Adverse Event form for any side-effects experienced.
- After the first episode of indigestion and heartburn, the participant will be asked to complete the same process for another 2 episodes within the 60-day study time frame; however, these are not required.
- If the participant completes the required assessments for a total of 3 episodes of indigestion and heartburn, they will be prompted, by email, to exit the study.
- If the participant only completes the required assessments for the required 1 episode of indigestion and heartburn, the participant will be prompted, by email, to complete the study exit form and will be exited from the study on day 60 (60 days from the day of receipt of the test product).
- Neither the sponsor nor Hawthorne Effect Inc. will not collect any unused test product.
- Upon receipt of study exit survey and review of completed study forms, participant will receive an Amazon gift card of $25 via email.

6.2. Study Schedule of Activities

Assessments	Screening	Consent	Before Receipt of Test Product	Test Product Received	Event 1	15 Minutes After Event Start	30 Minutes After Event Start	60 Minutes After Event Start
Study Window								
Screening Survey	X							
Consent		X						
Baseline Survey			X					
Demographics			X					
Acknowledgement of receipt of test product				X				
Symptom Diary					X			X
4-point Likert Scale					X	X	X	X
Test Product Consumed					X			
Medications & Supplements			X					
AE Assessment					X	X	X	X
Study Exit Survey								

Assessments	**Event 2**	**15 Minutes After Event Start**	**30 Minutes After Event Start**	**60 Minutes After Event Start**	**Event 3**	**15 Minutes After Event Start**	**30 Minutes After Event Start**	**60 Minutes After Event Start**	**Study Exit**
Study Window									
Screening Survey									
Consent									
Baseline Survey									
Demographics									
Acknowledgement of Receipt of Test Product									
Symptom Diary	X			X	X			X	
4-point Likert Scale	X	X	X	X	X	X	X	X	
Test Product Consumed	X				X				
Medications & Supplements									
AE Assessment	X	X	X	X	X	X	X	X	X
Study Exit Survey									X

6.3. Participant Enrollment and Follow-Up

Participants suffering from mild to moderate symptoms of indigestion and heartburn will complete a cloud-based, HIPAA-secured screening survey to determine eligibility. All eligibility criteria must be met for participants to be approved for enrollment in the study. Participants will be provided informed consent and the opportunity to ask questions related to the study procedures, risks and benefits, and rights related to participation in the study. Participants who sign the study informed consent will be prospectively enrolled in the study and provided a link to a patient portal, which provides study resources. Participants will take the study formula at the onset of symptoms and provide information related to symptoms of indigestion/heartburn during the follow-up period. A remote study coordinator may prompt participants to provide study information to ensure that the study forms are completed. Efforts will be taken to ensure minimal withdrawals and loss to follow-up.

6.4. Adverse Event and Safety Monitoring

Adverse Events (AEs) are defined as any untoward medical occurrences described by the study participant. All AEs will be self-reported and documented on the platform. The AEs will be reviewed by the study team including the remote trial coordinator and study principal investigator and reported according to the IRB requirements. Participants who experience adverse events will be advised to seek medical attention.

In the event that a participant experiences an adverse event, the clinical study manager or clinical ops coordinator will notify both the PI and Sponsor. The Sponsor will take appropriate action according to their standard operating procedures for any adverse events that warrant action by the sponsor.

6.4.1. Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with the test product (in high doses exceeding recommended use):

- Headache
- Amenorrhea
- Upset Stomach
- Diarrhea
- Hives
- Difficulty breathing
- Facial swelling
- Drowsiness
- Tiredness

- Vomiting

6.4.2. Adverse Event Relationship

Each reported AE will be assessed by the Investigator for relatedness, severity and causality.

6.4.3. Serious Adverse Events

A Serious Adverse Event is an Adverse Event that leads to death or to serious deterioration in the health of the participant that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or body function.

6.5. Lost to Follow-Up

If a participant fails to provide event information via the study/patient portal 30 days after the start of the trial, the remote coordinator will attempt to contact the participant to ascertain whether or not the participant has had an episode of indigestion or heartburn or not and if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study and the study exit form will be completed.

6.6. Test Product Packaging/Handling/Storage/Accountability

- The 3-episode supply of test product will be packaged and labeled with ingredients and a study ID number.
- Participants will receive guidance on how to report receipt, store, and use the test product.
- Hawthorne Effect Inc. will support storage and shipment of test product, documentation of test product assignment, and completion of test product accountability.

6.7. Study Management

This study uses a decentralized clinical trial format to foster inclusivity, diversity and accessibility for a broad study population and to ensure efficiencies for enrollment and study data collection. The study will be managed using an end to end virtual clinical trial platform called Hawthorne Effect Study Visit Management Platform which is designed to make patient participation in clinical trials more accessible and as least burdensome as possible. The Hawthorne Effect platform (www.hawthorne-effect.com) is GCP/ICH/21CFR and HIPAA compliant. Hawthorne Effect uses a network of specialty vetted and trained healthcare professionals, or HEROs who are study

investigators, screeners and conduct personalized patient visits for screening and follow-up. For this trial, the Hawthorne Effect study visits will be virtual, and the platform will be used to collect patient reported outcomes and to track screening, enrollment and study compliance.

7. Statistical Considerations

7.1. Study Outcomes Measures

Analysis populations:

The *intent to treat* (ITT) population consists of all participants who are consented, report the onset of indigestion and heartburn, and have taken the study medication at least once. The primary analysis will be in the ITT population.

Primary Endpoint:

The primary endpoint has two components, reduction in indigestion severity and reduction in heartburn severity. Participants will be asked to rate each symptom (bloating, early fullness during a meal, pain or discomfort in the upper abdomen, burning in the upper abdomen, pain/burning in the center of your chest, nausea, vomiting, burping) on a 4-point Likert scale at 4 time points: prior to taking the test product, 15, 30, and 60 minutes after taking the test product. The improvement in symptoms from baseline will be evaluated on a pairwise basis separately for each component and each time point. P-values will be computed for the improvement.

There is no control group for the primary analysis.

Secondary Endpoints:

Secondary endpoints will be gathered on the subjective experience of these participants related to general health, personal experience with the test product. The secondary endpoints will be self-reported by the participant on their online portal. There will be a questionnaire related to general health and the subjective experience of the participant administered at baseline and at study exit.

The purpose of the secondary analyses is to investigate the association between various baseline and other measurements and outcomes. These secondary analyses are considered hypothesis generating, and the descriptions are somewhat informal. The trial data may suggest secondary analyses not described here.

Secondary endpoints:

- The time to other intervention will be analyzed.
- A longitudinal analysis will be performed for participants who report on more than one incident of heartburn or indigestion.
- Adverse events will be summarized.
- An additional data presentation will consist of results from both Treatment and Control in similar studies appearing in the literature. There will be no formal statistical comparison of results from this study and historical studies.
- The Net Promoter Score will be summarized and compared against outcomes.
- Comparison against normal behavior will use the paired sample t-test.

7.2. Sample Size Considerations

Based on information from a variety of studies a highly pessimistic assumption is that there would be a mean improvement of 0.5 with a standard deviation of 1.5. (These values refer to the 4-point scale.) Based on these assumptions, a sample size of 97 participants would result in a 90% power to detect an improvement using the paired-sample t-test. If data from multiple incidents per participant are useful, the power to detect an improvement would increase. The final sample size of 200 participants has been chosen to allow for various contingencies, including uncertainties about compliance in this self-reported trial, and the fact that some participants may not experience heartburn or indigestion during the trial period.

It should be emphasized that these assumptions are for sample size purposes only. Trial analysis will use the data as collected.

As discussed above, the number 200 may be increased based on observed data concerning the number of participants with indigestion and heartburn. The actual outcomes of treated participants will not be considered in this analysis, merely whether or not enrolled participants have reported starting using the test product. The method of reevaluating the sample size will be described in the Statistical Analysis Plan.

7.3. Analysis Plan

Separate tables will be presented showing the changes from baseline for each component and each time point. The changes will be evaluated by the paired sample t-test. A longitudinal analysis will be performed for participants who report on more than one incident of heartburn or indigestion.

General statistical methods:

Data will be analyzed using standard statistical methods, as further specified in a statistical analysis plan (SAP), which will be prepared in detail later.

- Data analysis will largely consist of summary statistics and graphs. The only formal group comparisons will be in covariate analyses.
- For continuous variables data presentation will consist of means, confidence intervals computed using the *t*-statistic, medians, and interquartile ranges. Group comparisons will use *t*-tests or ANOVA.
- For discrete variables confidence intervals will use the exact intervals, where available. Group comparisons will use Fisher's exact test, with the Monte Carlo version used where computationally necessary.
- For time to event variables analysis will use the Kaplan-Meier algorithm, and group comparisons will use the log-rank or proportional hazards methods, depending on the data type.
- Visual analog scale values will be treated as continuous variables. Frequency counts will also be provided for scales with 10 or fewer distinct response levels.
- Covariate analyses will investigate the relation between baseline and outcome variables, using methods appropriate to the data types involved. Age, gender, and baseline medications will be included in these analyses where appropriate data are available.
- Present intention is that the analysis will be performed in R, and the precise form of algorithms will be the default of R. Kaplan-Meier, log-rank, and proportional hazards algorithms will be the defaults of the survival package.
- The exact items to be compared depend on what is reported in each historical control study. When possible, the items will include symptom relief at each time measured, including within-participant p-values, and time to the lowest level on a 4-point scale and to the lowest 2 levels on a 10-point scale. as well as reported baseline characteristics. When two-arm studies are compared, both arms will be reported in this comparison. In some studies, only indigestion or heartburn will be reported; when both are reported they will be separated for the comparison. Specific studies to be considered will be identified prior to the analysis of actual trial data.

8. Informed Consent Process

The study protocol and informed consent will be reviewed and approved by Advarra Institutional Review Board prior to study start.

Study candidates will learn about the study via digital advertisements. If interested in learning more, they will be referred to a website "landing page" that will provide detailed information about the study. They may opt to complete a screening survey ascertaining study eligibility through patient reported outcomes. If successfully completed (no exclusion criteria are selected), candidate will be invited to review the study consent form tutorial which includes the opportunity to ask questions related to the study from the Principal Investigator or delegated authority of the investigator. Candidate will be provided with contact information to reach investigator or study manager as desired.

Candidate may sign the informed consent via electronic signature as provided by Hawthorne Effect. The study manager will verify candidate signature prior to enrollment as a study participant.

9. Subject Confidentiality

All participants' data and personal information will be kept confidential. Only those involved with the study will have access to participant information. The data will be stored by Hawthorne Effect on a HIPAA compliant platform. The platform, which the data is stored on, will require a personalized username and password to gain access.

10. Publication

This study will be registered on clinicaltrials.gov prior to commencement of enrollment the results will be analyzed and submitted for publication.

11. Limitations

The study described in this protocol has some limitations. There is no concurrent control, as seems appropriate for the first study on this combination test product. The study relies solely on participants' subjective information and self-reporting; there is no medical review of symptoms, and no independent check on participant compliance. Some participant groups are not studied, including those under 18 years of age and pregnant women.

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13. Supplement and Appendix

13.1. 13.1 Appendices

13.1.1. Appendix A Drug Interactions

Drug Interactions for Test Product

DGL EXTRACT

There are no Serious Drug Interactions known for DGL Extract. Whereas Licorice contains a constituent glycyrrhizic acid, which can cause a syndrome of apparent mineralocorticoid excess when eaten in large amounts, DGL extract has the glycyrrhizic acid removed and so should not pose the same interactions as regular Licorice extract. Still, there are some potential Moderate Interactions, where DGL may interact in the metabolism of certain drugs (which utilize the same enzymes it inhibits), or other effects, such as estrogenic or diuretic effects. See Below for List.

CYTOCHROME P450 2B6 (CYP2B6) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

In vitro research shows that licorice extract and glabridin, a constituent found in the licorice species G. *glabra*, inhibit cytochrome P450 2B6 (CYP2B6) isoenzymes (10300,94822). Licorice extract from the species G. *uralensis* seems to inhibit CYP2B6 isoenzymes to a greater degree than G. *glabra* extract in vitro (94822). Theoretically, these species of licorice might

increase levels of drugs metabolized by CYP2B6; however, these interactions have not yet been reported in humans. Some drugs that are metabolized by CYP2B6 include ketamine (Ketalar), phenobarbital, orphenadrine (Norflex), secobarbital (Seconal), rifampin (Rifadin), and dexamethasone (Decadron). Use licorice cautiously or avoid in patients taking these drugs.

CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Licorice extracts from the species G. *glabra* and G. *uralensis* inhibit cytochrome P450 2C19 (CYP2C19) isoenzymes in vitro (94822). Theoretically, these species of licorice might increase levels of drugs metabolized by CYP2C19; however, this interaction has not yet been reported in humans. Some drugs metabolized by CYP2C19 include proton pump inhibitors including omeprazole (Prilosec), lansoprazole (Prevacid), and pantoprazole (Protonix); diazepam (Valium); carisoprodol (Soma); nelfinavir (Viracept); and others.

CYTOCHROME P450 2C8 (CYP2C8) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Licorice extract from the species G. *glabra* and G. *uralensis* inhibits cytochrome P450 2C8 (CYP2C8) isoenzymes in vitro (94822). Theoretically, these species of licorice might increase levels of drugs metabolized by CYP2C8; however, this interaction has not yet been reported in humans. Some drugs metabolized by CYP2C8 include amiodarone (Cardarone), paclitaxel (Taxol); nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Cataflam, Voltaren) and ibuprofen (Motrin); rosiglitazone (Avandia); and others.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is conflicting evidence about the effect of licorice on CYP2C9 enzyme activity. In vitro research shows that extracts from the licorice species G. *glabra* and G. *uralensis* moderately inhibit cytochrome P450 2C9 (CYP2C9) isoenzymes (10300,94822). However, evidence from an animal model shows that licorice extract from the species G. *uralensis* can induce hepatic CYP2C9 activity (14441). Reasons for these discrepancies are not clear. Until more is known, licorice should be used cautiously in people taking CYP2C9 substrates. Some drugs metabolized by CYP2C9 include celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), and warfarin (Coumadin).

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Pharmacokinetic research shows that the licorice constituent glycyrrhizin, taken in a dosage of 150 mg orally twice daily for 14 days, modestly decreases the area under the concentration-time curve of midazolam by about 20%. Midazolam is a substrate of cytochrome P450 3A4 (CYP3A4). This suggests that glycyrrhizin modestly induces CYP3A4 activity (59808). Evidence from animal research also shows that licorice extract from the species G. *uralensis* induces CYP3A4 activity (14441). However, licorice extract from G. *glabra* species appear to inhibit CYP3A4-induced metabolism of testosterone in vitro. It is thought that the G. *glabra* inhibits CYP3A4 due to its constituent glabridin, which is a moderate CYP3A4 inhibitor in vitro and not present in other licorice species (10300,94822). Until more is known, licorice should be used cautiously in people taking CYP3A4 substrates. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), clarithromycin (Biaxin), cyclosporine (Neoral, Sandimmune), diltiazem (Cardizem), estrogens, indinavir (Crixivan), triazolam (Halcion), and numerous others.

ESTROGENS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, licorice might interfere with estrogen therapy due to estrogenic and anti-estrogenic effects (7860,16058).

MIDAZOLAM (Versed, others)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

In humans, the licorice constituent glycyrrhizin appears to moderately induce the metabolism of midazolam (59808). This is likely due to induction of cytochrome P450 3A4 by licorice. Until more is known, licorice should be used cautiously in people taking midazolam. .

WARFARIN (Coumadin)

Interaction Rating = **Major** Do not take this combination.
Severity = High • Occurrence = Probable • Level of Evidence = **D**

Licorice seems to increase metabolism and decrease levels of warfarin in animal models. This is likely due to induction of cytochrome P450 2C9 (CYP2C9) metabolism by licorice (14441). Advise patients taking warfarin to avoid taking licorice.

Interactions with Herbs & Supplements

CARDIAC GLYCOSIDE-CONTAINING HERBS: Theoretically, the overuse or misuse of licorice can increase the risk of cardiotoxicity due to potassium depletion (10393). Cardioactive herbs include digitalis, lily-of-the-valley, pheasant's eye, and squill.

STIMULANT LAXATIVE HERBS: Theoretically, concomitant overuse or misuse of licorice

with stimulant laxatives can increase the risk of potassium depletion (10393). Stimulant laxative herbs include aloe, alder buckthorn, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge, gossypol, greater bindweed, jalap, manna, Mexican scammony root, rhubarb, senna, and yellow dock.

ARTICHOKE LEAF EXTRACT

There are no known Drug Interactions for Artichoke Leaf Extract.

None known.

Interactions with Herbs & Supplements
None known.

GINGER ROOT EXTRACT

There are no Serious Drug Interactions known for Ginger. There are some potential Moderate Interactions, where Ginger may cause a blood thinning effect which could interact with certain drugs. See Below for List.

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **B**

Based on laboratory research, ginger is thought to inhibit thromboxane synthetase and decrease platelet aggregation (7622,12634,20321,20322,20323,96257). However, this has not been demonstrated unequivocally in humans, with mixed results from clinical trials (96257). Theoretically, excessive amounts of ginger might increase the risk of bleeding when used with anticoagulant/antiplatelet drugs. Some anticoagulant or antiplatelet drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.

ANTIDIABETES DRUGS

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Moderate • Occurrence = Unlikely • Level of Evidence = **D**

Evidence from animal and human research suggests that ginger might increase insulin levels and/or decrease blood glucose levels (12636,20402,20403,20404,20405,89895,89896). Theoretically, ginger might have an additive effect with antidiabetes drugs and cause hypoglycemia. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta,

Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

CALCIUM CHANNEL BLOCKERS

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Moderate • Occurrence = Unlikely • Level of Evidence = **D**

Preliminary research suggests ginger might have hypotensive and calcium channel-blocking effects (12633). Theoretically, ginger might have an additive effect with calcium channel blockers. Calcium channel blockers include nifedipine (Adalat, Procardia), verapamil (Calan, Isoptin, Verelan), diltiazem (Cardizem), isradipine (DynaCirc), felodipine (Plendil), amlodipine (Norvasc), and others.

CYCLOSPORINE (Neoral, Sandimmune)

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

In an animal model, ginger juice taken 2 hours prior to cyclosporine administration reduced the maximum concentration and area under the curve of cyclosporine by 51.4% and 40.3%, respectively. This effect was not observed when ginger juice and cyclosporine were administered at the same time (20401).

METRONIDAZOLE (Flagyl)

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

In an animal model, ginger increased the absorption and plasma half-life of metronidazole. In addition, the elimination rate and clearance of metronidazole was significantly reduced (20350).

NIFEDIPINE

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Clinical research shows that combined treatment with ginger 1 gram plus nifedipine 10 mg significantly inhibits platelet aggregation compared to nifedipine alone or ginger alone (20324).

PHENPROCOUMON

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Phenprocoumon, a warfarin-related anticoagulant used in Europe, might increase the international normalized ratio (INR) when taken with ginger. There is one case report of a 76

year old woman with a stable INR on phenprocoumon that increased to greater than 10 when she began consuming dried ginger and ginger tea (12880).

WARFARIN (Coumadin)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **B**

Preliminary evidence suggests that ginger might inhibit thromboxane synthetase and decrease platelet aggregation (7622,12634,20321,20322,20323). In one case report, ginger increased the INR when taken with phenprocoumon, which has similar pharmacological effects as warfarin (12880). In another case report, ginger increased the INR when taken with a combination of warfarin, hydrochlorothiazide, and acetaminophen (20349). A longitudinal analysis suggests that taking ginger increases the risk of bleeding in patients taking warfarin for at least 4 months (20348). However, research in healthy people suggests that ginger has no effect on INR, or the pharmacokinetics or pharmacodynamics of warfarin (12881,15176). Until more is known, monitor INRs closely in patients taking significant amounts of ginger.

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Based on laboratory research, ginger is thought to inhibit thromboxane synthetase and decrease platelet aggregation (7622,12634,20321,20322,20323). However, this has not been demonstrated unequivocally in humans with mixed results from clinical trials (96257). Concomitant use of ginger with other herbs that might affect platelet aggregation could theoretically increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginkgo, Panax ginseng, red clover, turmeric, and others.

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Ginger might increase insulin levels and/or decrease blood glucose levels (12636,20402,20403,20404,20405,89895,89896). Theoretically, ginger might have additive effects with herbs that decrease blood glucose levels. Herbs with hypoglycemic potential include devil's claw, fenugreek, guar gum, Panax ginseng, and Siberian ginseng.

CHAMOMILE EXTRACT

There are no Serious Drug Interactions known for Chamomile. There are some theoretical Moderate Interactions, where Chamomile may interact in the metabolism of certain drugs (which utilize the same enzymes it inhibits), Chamomile might also exhibit an estrogenic activity, blood thinning activity or sedative effects that could have Moderate Interactions with certain drugs. See Below for List.

BENZODIAZEPINES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

German chamomile has mild sedative effects. Theoretically, concomitant use with benzodiazepines might cause additive effects and side effects (9765,12725,19719). Some benzodiazepines are alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), lorazepam (Ativan), midazolam (Versed), temazepam (Restoril), triazolam (Halcion), and others.

CNS DEPRESSANTS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

German chamomile has mild sedative effects. Theoretically, concomitant use with drugs with sedative properties can cause additive effects and side effects (9765,12725,19719). Some CNS depressants are benzodiazepines, pentobarbital (Nembutal), phenobarbital (Luminal), secobarbital (Seconal), fentanyl (Duragesic, Sublimaze), morphine, zolpidem (Ambien), and others.

CONTRACEPTIVE DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, concomitant use of large amounts of German chamomile might interfere with contraceptive drugs through competition for estrogen receptors (12728).

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

There is preliminary in vitro and in vivo evidence that German chamomile might inhibit cytochrome P450 1A2 (CYP1A2) (12734,19720). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP1A2 in patients taking German chamomile. Some drugs metabolized by CYP1A2 include amitriptyline (Elavil), haloperidol (Haldol), ondansetron (Zofran), propranolol (Inderal), theophylline (Theo-Dur, others), verapamil (Calan, Isoptin, others), and others. Use German chamomile cautiously or avoid in patients taking these drugs.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is preliminary in vitro evidence that German chamomile might inhibit cytochrome P450 2C9 (CYP2C9) (19720). So far, this interaction has not been reported in animals or humans. However, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients

taking German chamomile. Some drugs metabolized by CYP2C9 include nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Cataflam, Voltaren), ibuprofen (Motrin), meloxicam (Mobic), and piroxicam (Feldene); celecoxib (Celebrex); amitriptyline (Elavil); warfarin (Coumadin); glipizide (Glucotrol); losartan (Cozaar); and others. Use German chamomile cautiously or avoid in patients taking these drugs.

CYTOCHROME P450 2D6 (CYP2D6) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There i's preliminary in vitro evidence that German chamomile might inhibit cytochrome P450 2D6 (CYP2D6) (19720). So far, this interaction has not been reported in animals or humans. However, watch for an increase in the levels of drugs metabolized by CYP2D6 in patients taking German chamomile. Some drugs metabolized by CYP2D6 include tricyclic antidepressants such as imipramine (Tofranil) and amitriptyline (Elavil); antipsychotics such as haloperidol (Haldol), risperidone (Risperdal), and chlorpromazine (Thorazine); beta-blockers such as propranolol (Inderal), metoprolol (Lopressor, Toprol XL), and carvedilol (Coreg); tamoxifen (Nolvadex); and others. Use German chamomile cautiously or avoid in patients taking these drugs.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is preliminary evidence that suggests that German chamomile might inhibit the cytochrome P450 3A4 (CYP3A4) isoenzymes (6450,19720). Theoretically, German chamomile might increase levels of drugs metabolized by CYP3A4. However, so far, this interaction has not been reported in humans. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and numerous others. Use German chamomile cautiously or avoid in patients taking these drugs.

ESTROGENS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Theoretically, concomitant use of large amounts of German chamomile might interfere with hormone replacement therapy through competition for estrogen receptors (12728).

TAMOXIFEN (Nolvadex)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, large doses of German chamomile might interfere with tamoxifen because of its potential estrogenic effects (12728).

WARFARIN (Coumadin)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Taking German chamomile and warfarin together might increase the effects of warfarin and increase the risk of bleeding. In one case, a 70-year-old woman taking warfarin developed retroperitoneal hematoma and bilateral recti muscle bleeding along with an INR of 7.9 following ingestion of German chamomile tea 4-5 cups/day and use of a topical chamomile-based lotion applied 4-5 times daily (14309).

Interactions with Herbs & Supplements
HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES: German chamomile has mild sedative effects. Theoretically, concomitant use with herbs that have sedative properties might enhance therapeutic and adverse effects (9765,12725,19719). Some of these supplements include 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, scullcap, valerian, yerba mansa, and others.

MARSHMALLOW ROOT EXTRACT

There are no Serious Drug Interactions known for Marshmallow Root Extract. There are some theoretical Moderate Interactions, where Marshmallow Root may interact in the metabolism of certain drugs, have hypoglycemic, blood thinning, or diuretic effects which may also affect the activity of certain drugs. See Below for List.

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Animal research suggests that marshmallow flower extract has antiplatelet effects (92846). Theoretically, concomitant use of marshmallow and anticoagulant/antiplatelet drugs might lead to additive anticoagulant/antiplatelet effects, potentially increasing the risk for bleeding in some patients.

Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

ANTIDIABETES DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Animal research suggests that marshmallow can have hypoglycemic effects (62022). Theoretically, marshmallow might have additive effects with hypoglycemic therapy (4). Monitor blood glucose levels closely. Dose adjustments to antidiabetes drugs may be necessary. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

LITHIUM

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Marshmallow is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, marshmallow might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

ORAL DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

The mucilage in marshmallow might impair absorption of oral drugs (1,11,12,19).

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Animal research suggests that marshmallow flower extract has antiplatelet effects (92846). Theoretically, concomitant use of marshmallow with herbs and supplements with anticoagulant/antiplatelet effects might increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, red clover, turmeric, willow, and others.

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Animal research suggests that marshmallow may have hypoglycemic effects (62022). Theoretically, marshmallow might have additive effects when used with other herbs and supplements with hypoglycemic potential. This might increase the risk of hypoglycemia in some patients. Some herbs and supplements with hypoglycemic potential include alpha-lipoic acid, bitter melon, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.

13.1.2. Appendix B Instructions for Use

Instructions for Use
Upset Stomach Relief

This test product was created for support with indigestion and heartburn, combining Deglycyrrhizinated licorice (DGL), Artichoke Leaf, Marshmallow Root, Ginger, and Chamomile for comprehensive, yet gentle plant-based support with indigestion. This formula is designed to promote digestion and feelings of digestive comfort, but also to help build long-term digestive wellness.

Daily Dosage:

2 capsules contain:

Active Ingredients: Licorice Extract, Artichoke Leaf Extract, Chamomile, Marshmallow Root, Ginger.

Inactive Ingredients:Capsule (Hydroxypropyl Methyl Cellulose, Purified Water, Carrageenan, Potassium Chloride), Rice Hull Concentrate.

Directions: Take 2 capsules at the onset of symptoms up to three times daily for relief of your indigestion and heartburn symptoms.

***These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.**

13.1.3. Appendix C Screening Form

Screening

Please answer the following questions to the best of your abilities.

1. Are you at least 18 years old? (DOB?)
2. Do you suffer from symptoms of indigestion and/or heartburn (see severity index below)? (Y/N)
3. Have you ever been diagnosed with any chronic liver disease? (Y/N)
4. Have you ever been diagnosed with any chronic renal disease? (Y/N)
5. Are you pregnant or breastfeeding? (Y/N)
6. Do you have any allergies to any of the following? (Y/N)
    a. Licorice
    b. Artichoke leaf
    c. Marshmallow Root
    d. Ginger
    e. Chamomile
    f. Rice Hull Concentrate
    g. Carrageenan
    h. Cellulose Capsule
7. Do you have more than 10 alcoholic beverages per week? (Y/N)
8. Are you willing to try the test product for relief of your indigestion and heartburn symptoms? (Y/N)
9. Have you been prescribed any medication by your doctor for any GI disorder or medication that can affect the GI system? (Y/N)
10. Have you ever had surgery of the upper GI tract or abdominal surgery (with the exception of having your gallbladder or appendix removed)? (Y/N)
11. Are you currently taking any anticoagulation, blood-thinning, medication daily (aspirin, warfarin, etc.)? (Y/N)
12. Are you able to swallow pills? (Y/N)

Severity index

Dyspepsia: Dyspepsia Symptom Severity Index (DSSI)

Aims

To develop a self-report measure to quantify the severity of dyspepsia symptoms in clinical practice and research.

Dyspepsia symptom severity index (DSSI)
Scale/item
Dysmotility-like
1. Frequent burping or belching
4. Bloating
5. Feeling full after meals
6. Inability to finish normal-sized meals
7. Abdominal (belly) discomfort, without pain, after meals
8. Abdominal (belly) distension (feels as though you need to loosen your clothes)
12. Nausea before meals
13. Nausea after meals
14. Nausea when you wake up in the morning
15. Retching (heaving as if to vomit, with little result)
16. Vomiting
Reflux-like
3. Burping with bitter tasting fluid in throat
17. Regurgitation of bitter fluid into your mouth (reflux) during the day
18. Regurgitation (reflux) at night
19. Burning feeling in your chest (heartburn)
20. Burning feeling in your stomach
Ulcer-like
9. Abdominal (belly) ache or pain right after meals
10. Abdominal (belly) pain before meals or when hungry
11. Abdominal (belly) pain at night
Overall item

From Leidy NK, Farup C, Rentz AM, Ganoczy D, Koch KL. Patient-based assessment in dyspepsia: Development and validation of dyspepsia symptom severity index (DSSI). *Dig Dis Sci.* 2000;45:1172–1179. With kind permission of Springer Science and Business Media.

Comments

This is a self-administered questionnaire of 20 items. The numbers in the table state the following order of the items in the questionnaire. The grading of the items by the patient should be on a 0 (absent) to 4 (very severe) Likert scale. One global item is included in order to gather data on the patient's overall impression of his/her dyspepsia symptom severity.

A total score is represented by the mean across the three subscales (dysmotility-, reflux-, and ulcer-like symptoms).

References

Leidy NK, Farup C, Rentz AM, Ganoczy D, Koch KL. Patient-based assessment in dyspepsia: Development and validation of dyspepsia symptom severity index (DSSI). *Dig Dis Sci.* 2000;45:1172–1179.

13.1.4. Appendix D Baseline Form

Baseline

1. Demographics
    a. Race/Ethnicity (Black or African American, White, Asian, American Indian or Alaska Native, Native Hawaiian or another pacific islander, other: ____, do not want to share)
    b. Sex (M, F, or Do not want to share)
2. On average how often do you get Indigestion and Heartburn? (few times a year, once a month, A few times a month, once a week, 2-3 times a week, Everyday)
3. How long does it usually take for your symptoms to reach maximum intensity? (0-30 min, 31 min- 1 hour, +1 hour)
4. How long do your symptoms usually last without medication? (0-30 min, 31 min- 1 hour,, 1-2 hour, >2 hours, do not resolve)
5. How long do your symptoms usually last with medication? (0-30 min, 31 min- 1 hour,, 1-2 hour, >2 hours, Do not resolve)
6. On average how bad are your symptoms without medication? (1-10)
7. On average how bad are your symptoms with medication? (1-10)
8. What symptoms do you experience when you are having an episode of Heartburn/Indigestion? (Check all that apply)
    a. bloating
    b. early fullness during a meal
    c. pain or discomfort in the upper abdomen
    d. burning in the upper abdomen
    e. pain/burning in the center of your chest
    f. nausea
    g. vomiting
    h. burping
    i. other: _____
    j. None of the above

9. Do any of the following bring on or trigger your symptoms of indigestion or heartburn? (Check All That Apply)
    a. Overeating
    b. Eating too quickly
    c. Fatty/greasy foods
    d. Spicy foods
    e. Caffeine
    f. Alcohol
    g. Smoking
    h. Other: _____
    i. None of the above

10. Do you take medications to treat your symptoms? (yes/no)
    a. What medication do you take? (free response)
    b. how long do you wait before taking medication?
        i. Right away
        ii. Within an hour
        iii. 1-2 hours
        iv. >2 hours

13.1.5. Appendix E Symptom Diary

Please complete the following items during your first episode of Indigestion/Heartburn. We encourage you to complete the forms online in real time. However, if you cannot log into your patient portal at the time of your symptoms please complete these forms and log into your patient portal as soon as possible and complete the online forms.

Reminder: Do not take any other medications or supplements within the first hour of taking the test product.

Date of Onset: _____ Time of Onset: _____

Trigger (check all that apply): □ Overeating □ Eating too quickly □ Fatty/Greasy Food □ Spicy Food □ Caffeine □ Alcohol
□ Smoking □Other: _____ □None of the above □ I do not know

Time test product taken: _____

Please rate the following symptoms at the following time points. Circle one answer.

Onset (Prior to take the test product)

Bloating

0	1	2	3
No Symptom	Slight	Moderate	Severe

Early Fullness During a Meal

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain or Discomfort in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burning in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain/Burning in the center of your chest

0	1	2	3
No Symptom	Slight	Moderate	Severe

Nausea

0	1	2	3
No Symptom	Slight	Moderate	Severe

Vomiting

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burping

0	1	2	3
No Symptom	Slight	Moderate	Severe

Other

0	1	2	3
No Symptom	Slight	Moderate	Severe

15 Minutes after taking the test product

Bloating

0	1	2	3
No Symptom	Slight	Moderate	Severe

Early Fullness During a Meal

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain or Discomfort in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burning in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain/Burning in the center of your chest

0	1	2	3
No Symptom	Slight	Moderate	Severe

Nausea

0	1	2	3
No Symptom	Slight	Moderate	Severe

Vomiting

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burping

0	1	2	3
No Symptom	Slight	Moderate	Severe

Other:

0	1	2	3
No Symptom	Slight	Moderate	Severe

30 Minutes after taking the test product

Bloating

0	1	2	3
No Symptom	Slight	Moderate	Severe

Early Fullness During a Meal

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain or Discomfort in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burning in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain/Burning in the center of your chest

0	1	2	3
No Symptom	Slight	Moderate	Severe

Nausea

0	1	2	3
No Symptom	Slight	Moderate	Severe

Vomiting

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burping

0	1	2	3
No Symptom	Slight	Moderate	Severe

Other:

0	1	2	3
No Symptom	Slight	Moderate	Severe

60 Minutes after taking the test product

Bloating

0	1	2	3
No Symptom	Slight	Moderate	Severe

Early Fullness During a Meal

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain or Discomfort in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burning in the Upper Abdomen

0	1	2	3
No Symptom	Slight	Moderate	Severe

Pain/Burning in the center of your chest

0	1	2	3
No Symptom	Slight	Moderate	Severe

Nausea

0	1	2	3
No Symptom	Slight	Moderate	Severe

Vomiting

0	1	2	3
No Symptom	Slight	Moderate	Severe

Burping

0	1	2	3
No Symptom	Slight	Moderate	Severe

Other:

0	1	2	3
No Symptom	Slight	Moderate	Severe

After your symptoms resolveplease complete any of the following questions if applicable.

Did your symptoms resolve completely with the test product? Yes No Time of complete symptom resolution: _____

Did you need to take another medication: Yes No

Medication #1: _____ Dose: _____ Time: _____

Medication #2: _____ Dose: _____ Time: _____

Medication #3: _____ Dose: _____ Time: _____

Did your symptoms resolve completely with taking your alternative medication? Yes No

After taking the alternative medication, time of complete resolution of symptoms: _____

Did you experience any side effects after taking the test product? (Y/N) If yes, **Please fill out the Adverse Event form.**

13.1.6. Appendix F Study Exit Form

Study Exit

1. Please rate your overall experience with the test product.

0	1	2	3	4	5	6	7	8	9	10
Poor					Neutral					Excellent

1a. Why? (free response)

2. Do you feel that the test product helped with your indigestion and heartburn?

0	1	2	3	4	5	6	7	8	9	10
Not at all					Neutral					definitely

3. How likely are you to recommend the test product to your friends or family members?

0	1	2	3	4	5	6	7	8	9	10
Not Likely					Neutral					Extremely Likely

4. Do you feel that the test product helped your body cope with occasional heartburn, occasional acid indigestion, and upset stomach?

0	1	2	3	4	5	6	7	8	9	10
Not at all					Neutral					definitely

5. Is there anything else that you would like to let us know about your experience with the product (taste, smell, consistency, or other)? (y/n) → (free response)

6. Did the test product help prevent you from having to take any alternative medication for your symptoms? (y/n)

13.1.7. Appendix G Adverse Event Form

Upset Stomach AE document

1. Did you experience any side effects after taking the test product? Y/N
    a. If so, did you experience any of the following
        - itching, rash, hives, throat/lip/tongue swelling, wheezing
        - low blood pressure, fainting, chest pain, shortness of breath, palpitations, irregular heart beat
        - severe, persistent nausea, vomiting, diarrhea, or abdominal pain
        - difficulty urinating, decreased urination
        - fatigue, appetite loss, yellowing skin/eyes, itching, dark urine
        - severe joint/muscle pain
        - slurred speech, one-sided weakness of face, arm, leg, vision
        - abnormal bleeding from nose or gums
        - blood in urine, stool, vomit,
        - marked mood, cognitive, or behavioral changes, thoughts of suicide
        - Other:
2. Please give a description of the event
3. How soon after taking the test product did you experience the side effect?
4. What did you do to alleviate the side effect?
5. Did you have to go to the hospital or see a doctor for this side effect?
    a. Please describe any diagnosis or treatment that they provided.
    b. If you were seen in the hospital, please upload any discharge paperwork or other documents from the hospital.

13.1.8. Appendix H Test Product Insert

Welcome to the Upset Stomach Relief Trial!

We appreciate you taking the time to participate in this trial. As you may already know, the aim of this study is to measure the impact the test product has on your symptoms of indigestion and heartburn. Please take the time to read the following information below to become acquainted with the trial instructions.

Instructions upon Test Product Receipt:

1. Please log onto the study portal and acknowledge the receipt by completing the 'Start Form'
2. Enclosed in the study bag, please find a 3-episode supply of the test product.
3. You will take the test product the next time you have an episode of indigestion and heartburn and need to take something to relieve the discomfort.

Instructions Once Product Intake Begins:

1. The next time you have symptoms of indigestion and heartburn and feel the need to take the test product, you will FIRST start the symptoms diary (paper forms included in this package).
    - You will complete the date of the episode, the time the episode began, what triggered the episode, and check all the symptoms you are experiencing.
    - **REMINDER: DO NOT TAKE ANY OTHER MEDICATION/SUPPLEMENT DURING THE HOUR AFTER TAKE THE TEST PRODUCT.**
2. Next, you will rate all the severity of each symptom you are experiencing.
3. Take the test product (2 capsules) and record the time you take the test product.
4. Rate each of your symptoms again at 15, 30, and 60 minutes after taking the test product.
5. After your symptoms resolve , you should complete the symptom diary.
    - Record whether your symptoms completely went away with the test product, if so, record the approximate time your symptoms resolved.
    - Record whether you needed to take alternative medication to help with your symptoms (remember you are only allowed to take alternative medication 1 hour after taking test product).
    - Record the name, dose, and time you took the alternative medication.
    - Record whether your symptoms completely went away with the alternative medication you took and the approximate time this occurred.
6. If at any point after taking the test product you experience any side effects from the test product, please log into the study portal and complete an Adverse Event form.
7. After the first episode of indigestion and heartburn, you will be asked to complete the same process for another 2 episodes; although we encourage you to complete these steps for another 2 episodes, they are not required.

8. If you complete the required assessments for a total of 3 episodes of indigestion and heartburn, you will be prompted, by email, to exit the study and complete the study exit form.
9. If you only complete the required assessments for the required 1 episode of indigestion and heartburn, you will be prompted, by email, to complete the study exit form on day 60 (60 days from the day of receipt of the test product).
10. Upon receipt of study exit survey and review of completed study forms, you will receive an Amazon gift card of $25 via email.

Thank you again for participating in this trial!

If you have any questions, please contact:
Jerome Tonog, Clinical Study Manager
Jerome.tonog@hawthorne-effect.com

13.1.9. Appendix I Informed Consent

RESEARCH SUBJECT
INFORMED CONSENT FORM & HIPAA AUTHORIZATION

Sponsor / Study Title:	**HL Natural, Inc. / "Evaluation of the impact of the HL Natural, Inc. Upset Stomach Relief product on the reduction of symptoms in adults who suffer from mild to moderate indigestion and heartburn"**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

Experimental Subjects Bill of Rights

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject you have the following rights:

1. To be told what the study is trying to find out.
2. To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice.
3. To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes.
4. To be told if I can expect any benefit from participating, and, if so, what the benefit might be. 5. To be told of the other choices I have and how they may be better or worse than being in the study.
5. To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study.
6. To be told what sort of medical treatment is available if any complications arise.
7. To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study.
8. To receive a copy of the signed and dated consent form.
9. To be free of pressure when considering whether I wish to agree to be in the study.

If you have other questions, you should ask the investigator or any one on the research team. In addition, I may contact the Institutional Review Board, which is concerned with protection of volunteers in research projects.

WELCOME

Introduction

You are invited to participate in a research study that examines an investigational product for occasional indigestion and heartburn relief. The test product contains all-natural substances which have been combined and placed into a chewable tablet to be taken at the sign of indigestion. All participants will receive the test product as part of their participation in the study.

An investigational product is one that is not approved by the United States Food and Drug Administration (FDA).

Participation in this study is voluntary. Before you decide to participate please read this form carefully and ask the study staff for further information or clarification as necessary. Ask as many questions as required to fully understand what your participation will involve. Please do not sign and date this form unless you are fully satisfied with the answers you have received.

This form is called an *informed consent form* and it contains information regarding the purpose of the study, participation requirements, potential risks, potential benefits and how your protected health information (PHI) will be managed.

Please take as much time as you need to review the material and make an informed decision.

ABOUT THE STUDY

Background

Dyspepsia, also known as indigestion, is a common symptom that can have many different causes. It occurs in about 25 percent of the population each year, but most affected people do not seek medical care. Approximately 25 percent of people with indigestion have do have a medical cause. However, up to 75 percent of people have functional dyspepsia, which means that there is no underlying cause on diagnostic evaluation. People with this type of dyspepsia usually describe feeling bloated, feeling full early during a meal, and/or upper middle stomach pain/burning. Symptoms may be bad enough to limit usual activities. Some people may have nausea, vomiting, or heartburn; however, these symptoms are usually infrequent. The most common approach to treat occasional indigestion and heartburn is to use antacids to neutralize what is often believed to be an overproduction of stomach acid. This acid-blocking approach can perpetuate the problem when used over a long period of time. Acid blocking also has the

drawback of causing deficiencies in certain vitamins and minerals over time, such as calcium, because it prevents absorption.

Who can participate?

Participants who are at least 18 years of age and who suffer from indigestion and heartburn and who are otherwise in good health will be invited to be screened for the study. There will be about 200 participants in this study. All potential participants in the study must meet the rules of the study. These are called the inclusion-exclusion criteria. You will be asked to complete a few screening questions before you can be enrolled in the study. If you meet all the rules you may choose to participate in the study.

What is the purpose of the study?

The purpose of the study is to evaluate the impact of the test product on the symptoms of occasional indigestion and heartburn in adult men and women who suffer from occasional indigestion and heartburn.

How long is the study?

The duration of participation for each participant is expected to be the shorter of two outcomes: 1) 60 days after the study start or 2) after the participant completes the protocol assessments for 3 episodes of indigestion or heartburn.

Can I withdraw from the study?

Your participation in the study is voluntary. You may choose not to participate without penalty or loss of benefits. If you decide to participate you may change your mind at any time throughout the study without any penalty or loss of benefits. If you withdraw from the study, any data collected from you prior to your withdrawal may be used for study purposes however no data will be collected or used after your withdrawal. You will not be asked to return the test product.

The study doctor or the sponsor can stop your participation at any time, without your consent, for any reason.

What's in the test product capsule ?
Active Ingredients: Licorice Extract, Artichoke Leaf Extract, Chamomile, Marshmallow Root, Ginger

Inactive Ingredients: Capsule (Hydroxypropyl Methyl Cellulose, Purified Water, Carrageenan, Potasium Chloride), Rice Hull Concentrate.
The ingredients in the test product have been included because they are potentially beneficial in promoting digestion and feelings of digestive comfort.

When will I take the test product?

You will be asked to take the test product at the onset of your indigestion or heartburn episode. The onset is defined as the time you take the test product.

Instructions for taking the product are: take 2 capsules per episode. The test product may be used after each onset of episode, but not more often than three times per day.

What else will I be asked to do?

1. Complete the screening survey.
2. Sign and date the eConsent.
3. Complete a baseline survey that includes demographic information as well as information on what medication and supplements you currently take.
4. Receive test product, log into study portal and complete test product receipt form. This will mark the start of your participation in this study.
5. 1st indigestion or heartburn event: start your symptom diary, complete the 4-point Likert Scale in order to rank the severity of your symptoms.
6. Take test product after completing the scale and first part of the symptom diary.
7. Continue to fill out the 4-point Likert Scale for each symptom you are experiencing at 15 minutes, 30 minutes and 60 minutes after taking test product.
8. Write down any adverse or ill effects after taking the test product any time after taking the test product.
9. Once your symptoms resolve, complete the symptom diary.
10. Repeat steps 5-9 for event 2 and event 3 (this is encouraged but not required).
11. Note any final adverse events (side effects) and complete the exit form.
12. During the 1 hour after taking the test product, no medication or supplementation (including all CBD products) other than the test product should be taken for relief of indigestion and heartburn symptoms. Once the 1-hour report has been submitted you may take other medications if required and record that behavior as part of your diary entry.
13. Participants are asked to limit the consumption of alcohol beverages to less than or equal to two drinks per day, and to abstain from the use of cannabis for the duration of the study.

You will be exited from the study if you complete the required assessments for three episodes or 60 days after the study start date (the day you receive the test product). When you reach either of these milestones you will be prompted, by email, to exit the study.

Are there any potential risks?

Minimal risk is foreseen for participants through their participation in the study. All the ingredients composing the test product are Generally Recognized as Safe (GRAS) by the FDA for daily consumption at their present concentrations.

The potential risks seen with high doses (significantly higher than the dosage for the study) are:

- Headache
- Amenorrhea (not having a period)
- Upset Stomach
- Diarrhea
- Hives
- Difficulty breathing
- Facial swelling
- Drowsiness (excess sleepiness)
- Tiredness
- Vomiting

There are some potential drug interactions that have only been noted in animal trials or preliminary/pre-clinical trials. There may be other risks that are unknown.

What are the potential benefits?

You may experience relief from your indigestion and heartburn symptoms faster than otherwise experienced by taking the study tablet as directed. However, there is no guarantee that you will benefit from your participation in this study. Information learned from the study may help other people in the future.

New findings

Any new important information that is discovered during the study that may influence your willingness to continue participation in the study will be provided to you.

Alternatives

This research study is for research purposes only. The only alternative is to not participate in this study.

Compensation

If you complete the study, which includes all of the surveys and study forms, you will receive an Amazon gift card of $25.00 sent to your email, at the end of your participation in the study. You will not receive any other compensation.

There will be no charge to you for your participation in this study. The test product will be sent to each participant without any cost. Any leftover test product will not need to be returned.

Compensation for study related illness

If you experience an adverse health outcome as a result of participation in this research, you should seek immediate medical attention. As soon as possible after the incident contact the study doctor or study staff at the phone number listed on the first page of this form.

If your adverse health outcome is found to result from the product provided to you as part of this study, the study sponsor will compensate you for related medical care. By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

To pay medical expenses, the sponsor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

How will my information be protected?

The Health Insurance Portability and Accountability Act (HIPAA) describes how your Protected Health Information (PHI) may be used, disclosed and made accessible to you. You will be asked to logon to a secured internet site using a login code and a password. The platform (internet site) used for the data collection is HIPAA compliant, meaning your private information is protected by law.

In order to validate your identity, communicate with you, determine your eligibility and send you the test product, we will collect your name, address, phone number, email address, date of birth and some medical records. Through the surveys we will be collecting personal health information related to the study.

The information we collect will be kept confidential and will be used only for the purpose of this study. Only study staff who are involved in this study will have access to your PHI. All reports and communications released from this study will identify participants by an identification number only and will not contain identifying information. The overall results of the study may be published however the identity of participants will not be included.

Your right to access your PHI in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
You will be emailed a PDF copy of this signed and dated consent form. There may be risks of loss of privacy and confidentiality if the PDF copy of this consent form is viewed and/or stored on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena. Also, the PDF copy of the consent may not be able to be permanently removed from a PED.

Medical Release

By signing and dating this document, you authorize the study doctor, the research team, the FDA, Advarra Institutional Review Board, and/or other authorized members of the HL Natural, Inc. and Hawthorne Effect workforce to request, receive, use, and share all health information pertaining to your medical history, mental or physical condition and treatment received for the duration of your participation in this research study.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

If you decide not to sign and date this form, you will not be able to take part in the study.

You understand that the research team and other authorized member of the Hawthorne Effect workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements.

You understand that in all disclosures outside of Hawthorne Effect, you will not be identified by name, social security number, address, telephone number or any

other direct personal identifier unless disclosure of the direct identifier is required by law.

Your authorization to use and share your study records does not expire; however, in California and any other state that does require an expiration date, the authorization will expire 50 years after you sign and date this authorization document.

You understand that you may withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the study doctor at the address on the first page.

You understand that even if you withdraw your permission, the study doctor for the research study may still use your protected information that was already collected if that information is necessary to complete the study.

Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event (a bad effect) from being in the study.

If you withdraw your permission to use your protected health information for research that means you will also be withdrawn from the research study, but standard medical care and any other benefits to which you are entitled will not be affected. You can also tell us you want to withdraw from the research study at any time without cancelling the authorization to use your data.

You will receive a signed and dated copy of this form for your records.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

Whom to contact about this study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00037630.

Closing Statement

I have read and understand the information in this informed consent form. My questions (if any) have been answered to my satisfaction and I do not have any further questions or doubts about partaking in this study. All written and oral communication regarding this study were in a language I fully comprehend. My decision to participate in this study is voluntary. I hereby consent to participate in this study under the conditions described above.

An electronic copy of the signed and dated consent form will be sent to you as an email attachment. Be aware that electronic copies may not be readily removed from personal electronic devices. If the personal electronic device is shared with other users, lost or hacked the consent form may be revealed.

If you would like to request a paper copy of your consent as an alternative to the electronic copy, please inform study staff before signing and dating the consent.

AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PI	Principal Investigator
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee

SOP	Standard Operating Procedure
WHO	World Health Organization