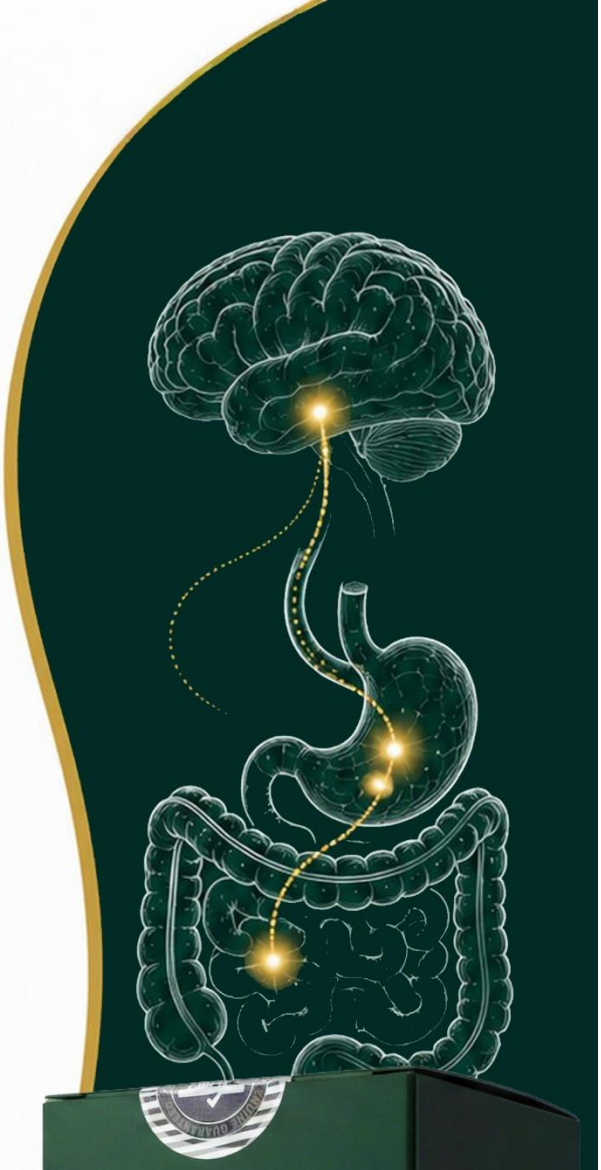
HyrboLife

Therapeutic Natural Innovation

GastroZEN

A NOVEL APPROACH TO THE NEUROGASTROENTERIC AXIS

Topical Cutaneous Neuromodulation to Restore Autonomic Balance and Improve Digestive Function



Science. Nature. Neuromodulation.

A new path to digestive well-being.

NATURAL FORMULA

12 botanical extracts carefully selected

VAGUS NERVE ACTIVATION

Supports autonomic balance via the cutaneous-visceral reflex

MULTIDIMENSIONAL EFFECT

Motor, secretory, immune, and psychological benefits

SCIENTIFIC BOOKLET

Evidence, mechanisms, and clinical applications

GastroZEN®
Mechanism of Action

Transcutaneous Peripheral Neuro-modulation via Cutaneous–Visceral Reflexes

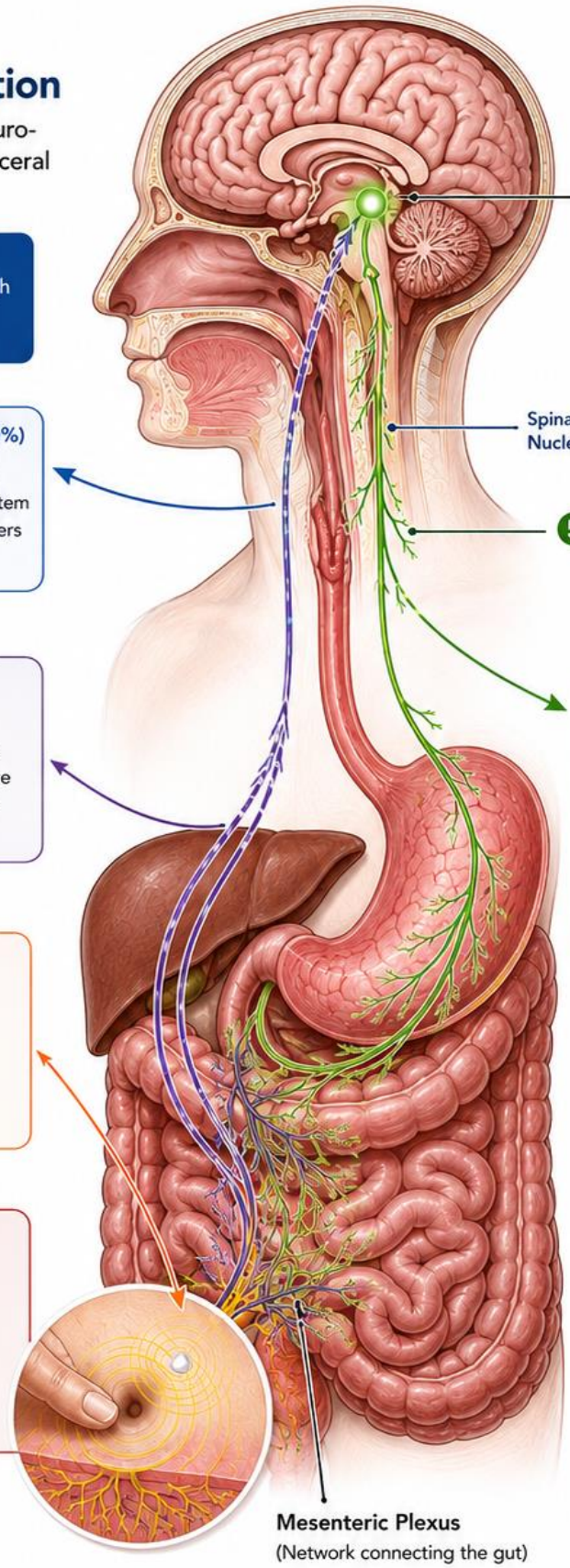
Therapeutic Goal
Restore autonomic balance through vagal activation → normalize GI motility, secretion and sensitivity.

1 Topical Application at the Umbilical Region
GastroZEN is applied topically around the umbilicus, targeting a high-density neurovascular zone connected to the mesenteric plexus.

2 Activation of Cutaneous Sensory Endings
The product stimulates specific cutaneous mechanoreceptors around the umbilicus (Aβ fibers: A6, C9).

3 Signal Conduction via Neural Pathways
Impulses travel through visceral afferent fibers of the vagus nerve and enter the brainstem via the nucleus tractus solitarius.

4 Afferent Signals to Brain (≈80%)
Sensory fibers transmit impulses via the vagus nerve to the brainstem and NTS, where autonomic centers are modulated.



4 Central Integration
Nucleus Tractus Solitarius (NTS)
- Receives afferent signals
- Modulates autonomic output
- Increases parasympathetic tone
- Inhibits sympathetic outflow

5 Vagus Nerve (X)
Main parasympathetic pathway to the gut (brain–gut axis)
- ~80% afferent (up to brain)
- ~20% efferent (from brain to gut)

6 Efferent (Parasympathetic) Output (≈20%)
Enhanced vagal activity to GI organs results in:
- ↑ Gastric & intestinal motility (↑ MMC)
- ↑ Digestive secretions
- ↑ Mucosal blood flow
- ↑ Visceral sensitivity threshold
- ↑ Anti-inflammatory (cholinergic pathway)
- ↓ Sympathetic overactivity

7 Physiological Outcomes
- ✓ Improve motility & evacuation
- ✓ Reduce bloating & gas
- ✓ Decrease visceral hypersensitivity
- ✓ Improve digestion & absorption
- ✓ Anti-inflammatory effect
- ✓ Restore autonomic balance (parasympathetic dominance)

8 Clinical Results
- ✓ Reduction of abdominal pain
- ✓ Decreased bloating & fullness
- ✓ Improved bowel habits
- ✓ Relief of reflux and dyspepsia
- ✓ Improved quality of life

Topical stimulation → Activation of cutaneous sensory endings → Afferent pathway (to brain) → Efferent pathway (vagal output) → Central autonomic modulation

SUMMARY FOR CLINICIANS

GastroZEN works by engaging a cutaneous–visceral reflex arc centered at the umbilical region. Stimulation of cutaneous afferents → activates vagal afferent fibers → modulates brainstem autonomic centers → enhances parasympathetic (vagal) output → normalizes GI function and reduces symptoms.

Key Points
- Non-invasive
- Drug-free
- Targets the root neurophysiology
- Safe and well-tolerated

Abstract

Functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome (IBS), functional dyspepsia, and functional gastroesophageal reflux disease (GERD), are increasingly recognized as disorders involving dysregulation of the gut–brain axis, impaired autonomic balance, visceral hypersensitivity, and persistent neuro-immune activation. Conventional therapeutic approaches often focus on symptomatic suppression without adequately addressing the underlying neural and functional disturbances contributing to chronic symptom persistence.

This report presents GastroZEN, a topical peripheral neuromodulation formulation designed to support restoration of autonomic gastrointestinal balance through activation of cutaneo-visceral reflex pathways via the periumbilical region. The proposed mechanism involves selective stimulation of cutaneous sensory receptors and ascending neural pathways associated with enhancement of vagal activity, increased parasympathetic output, modulation of gastrointestinal motility, and reduction of excessive sympathetic activation.

The physiological framework presented in this report integrates neuroanatomical modeling, autonomic regulation principles, and preliminary clinical observations collected under supervised clinical use. Reported findings demonstrated measurable improvement in gastrointestinal symptom patterns, enhancement of heart rate variability (HRV) parameters associated with vagal tone, improvement in visceral sensitivity measurements, and progressive stabilization of bowel function in functional gastrointestinal conditions.

GastroZEN is presented as an innovative peripheral neuromodulation approach intended to support functional gastrointestinal regulation through non-systemic reflex-based modulation of the gut–brain axis, offering a multidimensional strategy targeting motility, secretion, neuro-immune balance, and visceral regulation within a unified physiological framework.

Executive Summary

Functional gastrointestinal disorders represent a complex clinical challenge; symptoms persist in a large segment of patients despite exhausting traditional treatments, underscoring the need for a protocol that targets the "neural root" of the problem rather than merely suppressing overt symptoms.
This report presents GastroZEN, an advanced therapeutic innovation based on transcutaneous peripheral neuromodulation via cutaneo-visceral reflexes. The product works through topical application to the umbilical region to stimulate specific sensory nerve endings, generating ascending signals that reset vagus nerve activity, enhance parasympathetic output, and inhibit excessive sympathetic response. This mechanism helps restore overall regulatory balance of the gastrointestinal tract (motility, secretions, and visceral sensitivity).

Clinical Evidence & Field Results:

This approach is not based solely on theoretical assumptions but is grounded in a documented clinical observation record involving over 300 patients under direct medical supervision, in addition to the results of a randomized, controlled proof-of-concept study (detailed in Appendix 2). The quantitative data demonstrate substantial and measurable improvement in biomarkers, positioning GastroZEN as a fundamental pillar and standalone treatment option in specialized clinics.

Terminology / Glossary

Term	Scientific & Functional Definition
Gut-Brain Axis	A bidirectional communication system linking the central nervous system and the gastrointestinal tract via neural, hormonal, and immunological pathways.
Vagus Nerve	The tenth cranial nerve, the backbone of neuro-gut communication; carries 80% of ascending signals to the brain and 20% of descending signals to the gut.
Peripheral Neuromodulation	A physiological approach supported by quantifiable preliminary data targeting the resetting of neural signals via stimulation of peripheral nerve endings to help restore functional organ balance.
Parasympathetic System	Part of the autonomic nervous system known as the "rest and digest" state; responsible for enhancing digestive secretions and regulating intestinal motility.
Visceral Hypersensitivity	A state in which intestinal nerves become more responsive to normal stimuli, leading to pain and discomfort despite normal organic test results.
Migrating Motor Complex (MMC)	Periodic electrical activity that cleanses the small intestine of food residue and bacteria between meals, preventing bacterial overgrowth (SIBO).
Cholinergic Anti-inflammatory Pathway	A mechanism by which vagus nerve activation reduces pro-inflammatory cytokine production and modulates local immune response.
Periumbilical Region	The area surrounding the umbilicus, characterized by anatomical specificity where remnants of fetal vessels and dense neural connections to the mesenteric plexus converge, providing an ideal entry point for reflex neuromodulation without the need for systemic absorption.

Term	Scientific & Functional Definition
Proton Pump Inhibitors (PPIs)	Drugs that suppress acid secretion, but their chronic use may lead to lower esophageal sphincter (LES) dysfunction and drug dependence.
Rome IV Criteria	A global diagnostic system for functional GI disorders, now termed: Disorders of Gut-Brain Interaction.
Globus Sensation	A persistent feeling of a "lump" or foreign body in the throat without an actual obstructive cause; often due to nerve irritation from non-acid reflux or the enzyme pepsin.

1. Clinical Introduction:

Moving Beyond Symptom Suppression Toward Targeting Neural Dysregulation

1.1. Epidemiological & Clinical Context

Functional gastrointestinal disorders, foremost among them irritable bowel syndrome (IBS) and Functional Dyspepsia (FD), represent a massive epidemiological burden on healthcare systems worldwide, with an estimated prevalence according to Rome IV criteria ranging between 10% and 25% of the population. In daily practice, this burden manifests as chronic symptoms including bloating, abdominal pain, heartburn, and disordered defecation—symptoms that are often not matched by organic signs detectable via endoscopy or imaging.

Despite the temporary efficacy of traditional treatments such as Proton Pump Inhibitors (PPIs) and prokinetics, a significant proportion of patients (20-35% according to studies) continue to suffer. The reason for this is not merely inadequate acid suppression or motility modification, but rather that these approaches target secondary consequences of the dysfunction while leaving the root cause unaddressed: the regulatory disruption of the neuro-gut axis—a dysfunction that has been shown to be physiologically detectable and quantifiable (see Appendices 1 and 2).

1.2. Neural Dysfunction as the Root Cause: A Modern Physiological Perspective

Mounting physiological evidence indicates that the core functional impairment in these patients lies at the level of the autonomic nervous system, specifically in reduced parasympathetic activity (vagal tone) and sympathetic hyperactivity. This dysfunction is not mere conjecture; it is an objectively measurable phenomenon via heart rate variability (HRV) analysis, representing the primary physiological target of GastroZEN. Its improvement has been quantitatively documented in the proof-of-concept study (Appendix 2, where HF-HRV increased by 20-35% within 30 minutes of application). This dysfunction translates clinically into:

- **Impaired digestive secretions:** Reduced physiological secretion of gastric acid, enzymes, and protective mucus, thereby impairing initial digestion and predisposing to a fermentative environment.
- **Impaired gut motility:** Weakness of the migrating motor complex (MMC), the small intestine's self-cleaning mechanism between meals, leading to content stasis and gas-producing bacterial overgrowth (SIBO).
- **Visceral hypersensitivity:** Lowered neural pain threshold, where normal physiological stimuli (e.g., mild distension) are converted into sharp pain signals.

These three mechanisms together form a vicious cycle that makes symptoms chronic and resistant to symptomatic treatments. Therefore, any effective intervention must target the highest common factor: restoring autonomic neural balance—precisely what the data in Appendices 1 and 2 indicate GastroZEN is capable of achieving.

1.3. Limitations of the Traditional Treatment Model:

Upon reviewing the mechanism of action of conventional therapies, it becomes clear that most target a single symptom of the dysfunction without addressing the deeper regulatory mechanisms. Proton Pump Inhibitors (PPIs), although effective at reducing hydrogen ion secretion, do not affect gut motility or lower esophageal sphincter (LES) function. Similarly, antibiotics, although they eradicate H. pylori, do not prevent symptom persistence in a subset of patients due to factors linked to the gut-brain axis. This limitation highlights the need for new therapeutic approaches that target the resetting of neural signals and broader functional regulation, which is proposed within the scientific evaluation framework of the GastroZEN preparation.

1.3.1 Chronic Use of Proton Pump Inhibitors (PPIs):

Clear gaps exist in the mechanism of action of Proton Pump Inhibitors (PPIs). These limitations are summarized in the following points :

- **Valve and Digestive Enzyme Dysfunction:**
  - These treatments merely modify gastric chemistry but do not address the underlying problem—lower esophageal sphincter (LES) relaxation. Studies confirm that up to 40% of patients do not achieve adequate improvement because gastric fluids continue to reflux toward the larynx and pharynx, carrying the enzyme pepsin.
  - When pepsin reaches the throat, it adheres to tissues and becomes inactive in the non-acidic environment. However, upon consuming foods or drinks with low pH such as apples (pH 3.3–4.0), yogurt (pH 4.4–4.8), or coffee (pH 4.8–5.1), the necessary acidic medium becomes available to reactivate the enzyme, which then immediately begins breaking down proteins within the tissues to which it had adhered. This repeated damage explains the patient's persistent complaint of globus sensation despite tests showing normalized gastric acidity.
  - **References:**
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC6297633
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC3801364
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC5137314
    - https://pubmed.ncbi.nlm.nih.gov/17417109
- **Rebound Acid Hypersecretion: Difficulty Weaning the Patient Off the Drug:**
  - Long-term acid suppression induces compensatory changes that render the patient physiologically dependent on the drug. Upon discontinuation, rebound acid hypersecretion occurs, hindering weaning protocols and forcing the physician to renew the prescription.
  - **References:**
    - https:/pubmed.ncbi.nlm.nih.gov/19362552
- **Secondary Health Issues (e.g., Bacterial and Fungal Overgrowth in the Gut):**
  - Continuously preventing gastric acid secretion disrupts the "acid barrier," the body's first line of defense. This disruption allows microbes to multiply abnormally within the small intestine; these drugs increase the likelihood of developing small intestinal bacterial overgrowth (SIBO) by 71%. These drugs are also a major risk

factor for fungal overgrowth (SIFO) as a result of reduced gastric acidity, which normally prevents their passage into the intestines.

- Additionally, the absence of acid renders the stomach unable to destroy parasite cysts (e.g., Giardia), facilitating their transmission to the intestines. The risk of infection with dangerous Clostridium bacteria also rises by 74%, along with a 73% increased likelihood of developing respiratory infections. These findings suggest the possible emergence of new symptoms in the patient (such as bloating and dyspepsia) as a result of complications that may be more severe than the original acid problem
- **References:**
  - https://pubmed.ncbi.nlm.nih.gov/28770351
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC3764612
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC10159235
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC3732842
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC5643276

– **Comprehensive Risks and Responsibility Toward the Patient:**

- Recent studies link long-term use of Proton Pump Inhibitors (PPIs) to an increased risk of chronic kidney disease, raising the likelihood of kidney failure by 20% to 50%. This risk places physicians before ethical challenges in balancing therapeutic benefits against risks, mandating adherence to scientific standards and the search for safe alternatives to protect vital organs. These findings put the physician in a difficult position, as they show that controlling acidity does not necessarily protect the patient from systemic complications; rather, it may be associated with a silent increase in the risk of chronic kidney failure. The study also demonstrated that twice-daily use doubles the risk compared to a single daily dose.
- **References:**
  - :https://pubmed.ncbi.nlm.nih.gov/26752337

– **Nutrient Deficiencies and Bone Weakness:**

- The impact of these medications does not stop at acid suppression; it extends to impairing the absorption of essential nutrients. These drugs are associated with a 65% increased risk of vitamin B12 deficiency and approximately a 43% increased risk of magnesium deficiency due to malabsorption, in addition to folic acid. With continued treatment, results from the Women's Health Initiative (WHI) showed that chronic PPI use is associated with a 47% increased risk of vertebral fractures, a 26% increased risk of wrist fractures, and a 25% increased risk of total fractures. This deficiency is not limited to its effect on bones and osteoporosis; it may also impact reproductive capacity—it can affect sperm quality in men or the regularity of hormonal cycles in women, raising questions about the role of these drugs in some cases of "unexplained infertility." Here, the physician faces a patient whose acidity has improved but who begins to suffer from fatigue, numbness, mineral disorders, and fertility issues—transforming the drug from a simple solution into a source of new health burdens requiring additional follow-up.
- **References:**
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC6463334
  - https://pubmed.ncbi.nlm.nih.gov/24327038
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC4181956
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC4240017
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC4110863

– **Reaching a "Dead End" in Treatment:**
  - Studies indicate that 40% of patients experience persistent symptoms with prolonged PPI use, and 44% suffer from difficulty discontinuing the drug due to acid rebound, necessitating alternative strategies.
  - **References:**
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC9072476
    - https://pubmed.ncbi.nlm.nih.gov/23311977
– **Cardiovascular Risks (Especially in Older Adults):**
  - Studies have shown that long-term use of these medications in older adults, particularly postmenopausal women, may be associated with an increased risk of heart disease and stroke. This is partly attributed to drug interactions with natural substances in the body that protect the arteries, in addition to its effect on the efficacy of certain common cardiac medications. This situation calls for a careful balance between symptomatic benefit and potential cardiovascular risks in this age group.
  - **References:**
    - https://pubmed.ncbi.nlm.nih.gov/39739511/

Pathological Axis	Associated Pathological Mechanism	Therapeutic Gap with PPIs	Rapid Clinical Reflection	Clinical Illustration (Direct Examples)
GERD (Gastroesophageal Reflux Disease)	Weak LES + mechanical reflux	Mechanical barrier not repaired	Partial improvement without addressing root cause	Heartburn reduced but persistent globus sensation
LPR (Laryngopharyngeal Reflux)	Pepsin deposition in tissues	Pepsin unaffected by PPIs	Persistence or shift of symptoms	Hoarseness, chronic cough despite acid control
Chronic PPI Use Disorders	Chronic acid suppression	Rebound upon withdrawal	Drug dependence; difficult weaning	Improvement during use; heartburn returns after stopping
Microbiome Dysbiosis	Loss of acid barrier	SIBO / Dysbiosis	Emergence of new symptoms	Bloating, gas, chronic diarrhea after therapy
Absorption Disorders	Non-acidic medium	Impaired Mg / B12 / Ca absorption	Micronutrient deficiency manifestations	Muscle cramps, osteoporosis, high fracture risk
Intestinal Infections	Weakened gastric immune defense	Increased infection susceptibility	Recurrent infections after antibiotics	Recurrent diarrhea, suspected C. diff
Chronic Functional Disorders	Multifactorial dysfunction (acid + motility + enzymes)	Only chemical treatment	Partial improvement without function restoration	Slow digestion, fluctuating symptoms despite acid reduction
Fertility & Hormones	Micronutrient deficiencies	Possible impact on fertility	Menstrual or sperm quality disturbances	B12 deficiency, hormonal imbalances
Older Adults (Cardiometabolic)	Drug interactions + cardiac effects	Increased risk of bleeding or heart disease	Need to balance benefit vs. risk	Elderly patient on Clopidogrel + PPIs, concern over cardiac risk

Based on the data presented in the table above, it is evident that some cases do not achieve a complete response from acid reduction alone, especially when symptoms persist or recur. Recent literature suggests that additional factors such as microbiome balance, absorption efficiency, and gut-brain axis regulation contribute to the variability in therapeutic response.

1.4. The Neurogenic Pathological Model: Autonomic Dysregulation as the Basis of Functional Symptoms

In light of the preceding data, it becomes clear that the most accurate explanation for these disorders does not view them as mere "symptoms without an organic cause," but rather understands them as a direct consequence of autonomic nervous system dysregulation—a dysfunction that is no longer a theoretical assumption but an observable and quantifiable phenomenon, as confirmed by the heart rate variability (HRV) and Barostat pressure data presented in Appendices 1 and 2. This model transcends the traditional (organic/functional) dichotomy to provide a unified physiological framework.

The central element of this model is the gut-brain axis, in which the vagus nerve—responsible for 80% of ascending signals from the gut to the brain—serves as the connecting link between the central nervous system and gastrointestinal functions. When the balance of this axis is disrupted due to factors such as chronic stress, infections, or prolonged use of suppressive medications, three interconnected and physiologically documented pathological mechanisms emerge, together forming the physiological basis of the symptoms:

- **Parasympathetic Underactivity:**
  This is the core dysfunction, measurable via reduced heart rate variability (HRV) parameters. In the proof-of-concept study (Appendix 2), this reduction was documented in patients before treatment, followed by a 20-35% increase within 30 minutes of GastroZEN application, confirming that this dysfunction can be targeted and modulated. This weakness results in:
  - Reduced protective digestive secretions (mucus, bicarbonate).
  - Impaired bile flow and pancreatic enzyme secretion.
  - Slowed gut motility, prolonging food transit time and predisposing to stasis and fermentation.

- **Visceral Hypersensitivity:**
  Arises from disordered processing of ascending sensory signals from the gut at the level of the spinal cord and brainstem, where the pain threshold is lowered. Natural stimuli—such as mild distension or peristaltic motion—are centrally interpreted as pain signals, explaining the severity of symptoms despite normal test results. This dysfunction was objectively measured in Appendix 2 via Barostat, where patients' pain threshold was markedly low before treatment (140 ± 15 mL).

- **Neuro-immune Dysregulation:**
  Loss of balance between the sympathetic and parasympathetic systems leads to dysfunction of the cholinergic anti-inflammatory pathway, allowing local inflammation of the intestinal mucosa to persist, increasing intestinal permeability and perpetuating the inflammation-pain cycle. This inflammation is chemically reflected in elevated fecal calprotectin (142 ± 22 µg/g in the GastroZEN group before treatment, as shown in Appendix 2).

Clinical Conclusion : Optimal therapeutic intervention lies not in silencing each symptom individually, but in targeting the highest common factor: restoring autonomic neural balance by

activating parasympathetic pathways and inhibiting excessive sympathetic response. This is the physiological foundation upon which GastroZEN is designed as a peripheral neuromodulation tool—precisely what the data in Appendices 1 and 2 indicate it can achieve: restoring autonomic balance (increased HRV), raising the visceral pain threshold (Barostat volume increase from 140 to 320 mL), and extinguishing local inflammation (calprotectin returning to normal levels).

2. Pathophysiology: The Gut-Brain Axis and the Vagus Nerve

2.1. Functional Anatomy of the Neuro-Gut Communication Axis:

The gut-brain axis represents a highly specialized bidirectional communication system that integrates neural, hormonal, and immunological signals to connect the central nervous system with the gastrointestinal tract. The vagus nerve is the primary component of this axis, carrying approximately 80% of ascending signals from the gut to the brain and 20% of descending signals from the brain to the viscera.

Anatomical Origin:
The vagus nerve arises from two main nuclei in the brainstem:

- **Dorsal Motor Nucleus of the Vagus:** Responsible for efferent parasympathetic signals to most gastrointestinal organs.
- **Nucleus Ambiguus:** Responsible for innervating the pharyngeal and esophageal muscles, controlling swallowing and speech.

The nerve then extends through the neck and chest to reach the abdominal organs, giving off branches to the esophagus, stomach, small intestine, and ascending colon.

Functional Fiber Diversity and Its Clinical Significance:
The vagus nerve is characterized by three types of fibers, the functional integration of which explains why targeting this nerve represents a multidimensional therapeutic strategy:

- **Afferent Fibers:** Constituting the vast majority (80%), they transmit real-time information to the brain about the chemical and mechanical state of the gut (distension, acidity, nutrients). These signals form the brain's "sensory awareness" of the gastrointestinal status moment by moment.
- **Efferent Fibers:** Transmit commands from the brain to smooth muscles and digestive glands via the neurotransmitter acetylcholine, regulating intestinal motility (peristalsis) as well as gastric, pancreatic, and biliary secretions.
- **Neuro-immune Fibers:** Form the basis of the "cholinergic anti-inflammatory pathway," responding to inflammatory signals coming from the gut by releasing local acetylcholine, which inhibits the secretion of pro-inflammatory cytokines (e.g., TNF-α), thereby limiting and controlling the severity of inflammation

This functional integration definitively explains why any dysfunction of the vagus nerve leads to a wide range of interconnected gastrointestinal symptoms (impaired motility, secretory dysfunction, loss of inflammatory control). It also explains why restoring its normal activity is a logical intervention that does not treat a single symptom but rather restores the gut's autonomic regulatory balance. This very point will be built upon in the next section to explain how GastroZEN achieves this goal physiologically.

.

2.2. The Role of the Vagus Nerve in Digestive Regulation: The Triple Interaction (Vagus – HPA Axis – Autonomic Nervous System)

The role of the vagus nerve is not limited to improving gastrointestinal functions; its regulatory influence extends to central neuro-hormonal axes. This triple interaction between the vagus nerve, the HPA axis (stress axis), and the autonomic nervous system definitively explains why activating this nerve leads to clinical improvements that go beyond the gut to include mood, sleep quality, and the overall response to psychological stress.

- **Inhibition of the HPA Axis:** Ascending signals from the vagus nerve reach the nucleus tractus solitarius (NTS) in the brainstem, the first central relay for processing visceral information. There, these signals stimulate interneurons that release the inhibitory neurotransmitter GABA, which in turn suppresses the activity of hypothalamic cells and stops the release of corticotropin-releasing hormone (CRH). The result is a cascade of sequential inhibition leading to a tangible reduction in cortisol levels (the stress hormone), thereby breaking the chronic stress cycle that is one of the primary drivers of functional gastrointestinal disorders.
- **Restoring Autonomic Balance (The "Cholinergic Brake"):** The vagus nerve acts as a natural "cholinergic brake" on the sympathetic nervous system (responsible for the "fight or flight" response). When parasympathetic activity increases, acetylcholine released from vagal nerve endings automatically inhibits sympathetic activity via a mechanism of reciprocal inhibition at two levels:
    - **Centrally:** In the brainstem and spinal cord, where preganglionic sympathetic neurons are inhibited.
    - **Peripherally:** In the enteric nerve plexuses, where it reduces the release of norepinephrine (the sympathetic neurotransmitter).

  This dual inhibition ensures a complete physiological transition from a state of sympathetic dominance (stress, spasm, reduced blood flow) to a state of parasympathetic dominance (relaxation, digestion, adequate perfusion).

- **Physiological-Clinical Shift:** From "Fight or Flight" to "Rest and Digest": The shift resulting from restored autonomic balance moves the body from a state of constant alarm (fight or flight) to a state of repair and renewal (rest and digest). Clinically, this transition translates into a series of observable improvements: decreased heart rate and blood pressure, increased blood flow to the gastrointestinal tract, improved coordination of gut motility and digestive secretions, and reduced systemic inflammatory response.

This triple interaction is the cornerstone that explains why targeting the vagus nerve via peripheral neuromodulation—as GastroZEN does—represents a multidimensional therapeutic intervention. It does not merely "suppress" an isolated symptom; rather, it reshapes the neuro-hormonal environment, allowing the gastrointestinal tract to naturally and sustainably restore its functional efficiency.

2.3. States of Vagus Nerve Dysregulation:

The following table illustrates the relationship between the types of dysfunctions in the gut-brain axis and their associated clinical expressions and physiological mechanisms:

Type of Dysfunction	Clinical Expression	Physiological Mechanism
Parasympathetic Underactivity	Slow digestion, constipation, poor appetite	Reduced protective gastric secretions, weak migrating motor complex (MMC), pancreatic enzyme insufficiency, and impaired coordination of bile flow (biliary dyssynergia).
Sympathetic Hyperactivity	Intestinal cramps, diarrhea, heartburn	Uncoordinated rapid transit (rapid transit), inappropriate transient lower esophageal sphincter relaxations (TLESRs) that increase gastroesophageal reflux.
Neuro-immune Dysregulation	Low-grade chronic inflammation, food sensitivity, bloating	Elevated pro-inflammatory cytokines (e.g., TNF-α), increased intestinal barrier permeability, and abnormal mast cell activation.
Visceral Hypersensitivity	Exaggerated abdominal pain, early bloating	Lowered pain threshold in the spinal cord and higher centers, where normal physiological stimuli (e.g., distension) are interpreted as sharp pain signals (allodynia and hyperalgesia).

Clinical Importance:

These four mechanisms together form a vicious cycle. For example, vagal weakness leads to food stasis and fermentation, which fuels inflammation and hypersensitivity. Targeting the common factor—restoring autonomic balance—is what gives a single therapeutic intervention (such as GastroZEN) the ability to dismantle this cycle at its roots, rather than chasing each symptom individually.

2.4. Clinical Application: How Vagus Nerve Dysfunction Explains Functional Disorders

Having established the role of the vagus nerve as a master regulator of autonomic balance, this understanding can now be applied directly to the most common functional disorders encountered in clinical practice. In each of the following conditions, the symptoms do not appear as isolated events but rather as predictable consequences of dysfunction in the neural signals that coordinate gastrointestinal work.

Irritable Bowel Syndrome (IBS)

In IBS, poor autonomic regulation emerges as a common factor linking the diverse symptoms (constipation, diarrhea, pain, bloating). Objective measurements (such as HRV analysis) reveal chronically reduced parasympathetic activity (vagal tone) and increased sympathetic activity. This dysfunction translates clinically into three interconnected manifestations:

- **Impaired intestinal cleansing:** Weak vagal signals lead to dysregulation of the migrating motor complex (MMC) periodicity, which is responsible for cleansing the small intestine between meals. The result is content stasis, causing bloating and predisposing to small intestinal bacterial overgrowth (SIBO).
- **Visceral hypersensitivity:** At the level of the spinal cord and brainstem, there is a disorder in processing ascending sensory signals from the gut. Instead of normal physiological stimuli (such as bowel distension by gas) being "filtered out," they are amplified and translated into

sharp pain signals. This lowered pain threshold is due to the absence of the vagus nerve's inhibitory effect, leaving enteric nerves in a state of neuronal hyperexcitability, so they respond painfully to stimuli that were previously below the threshold of conscious perception (sub-threshold).

Functional Dyspepsia and Gastroesophageal Reflux Disease (GERD)

This disorder particularly illustrates the vagus nerve's role as a mediator linking "gastric chemistry" and "valve mechanics." Physiologically, tight closure of the lower esophageal sphincter (LES) depends on the vagus nerve sensing the optimal gastric acidity (pH 1-3). When this level is reached, the nerve sends a signal that increases LES contraction strength. Any disruption in this loop leads to direct consequences:

- **Lack of adequate acidity:** Whether due to natural deficiency or prolonged PPI use, this eliminates the primary trigger for the vagus nerve, weakening the efferent signal to the valve, causing it to relax and increasing reflux—not due to excess acid, but due to mechanical closure weakness.
- **Poor coordination of gastric emptying:** Weak parasympathetic signals slow gastric emptying, causing early satiety, nausea, and dyspepsia.

Helicobacter pylori (H. pylori)

To understand the virulence of H. pylori, it is essential to consider the host environment regulated by the vagus nerve. The nerve is responsible for the stomach's two main lines of defense: protective mucus secretion and regulation of gastric wall blood perfusion. When parasympathetic activity weakens, the efficiency of these mucus defenses and blood perfusion declines, creating conditions that transform bacterial presence (which might otherwise be silent) into active infection. This explains why some patients continue to experience inflammation and symptoms even after the bacterium has been eradicated with antibiotics—because the neural dysregulation and associated local inflammation may persist.

Accompanying Psychological Expressions

The accompanying psychological symptoms (anxiety, stress, sleep disturbance) reflect the other side of gut-brain axis dysfunction. The vagus nerve acts as a direct communication channel, transmitting "safety signals" from the body to brain regions responsible for processing emotions, such as the amygdala and hippocampus. Physiologically, its activation has been shown to inhibit the HPA axis and reduce cortisol levels. When these signals weaken, the brain loses this natural inhibition, leading to HPA axis hyperactivity, which clinically translates into excessive anxiety and fear, thereby fueling a vicious cycle of worsening physical symptoms.

2.5. Therapeutic Hypothesis: Restoring Autonomic Balance as an Intervention Goal

Based on the preceding physiological model, it is clear that functional disorders are not merely isolated symptoms but rather the product of a vicious cycle that begins with weak parasympathetic signals and ends with disrupted motility, secretion, and inflammation. Optimal treatment, therefore, lies not in targeting each symptom individually, but in targeting the common factor that drives the entire cycle—namely, restoring autonomic neural balance. This can be achieved through three integrated therapeutic axes:

- **Activation of ascending cholinergic pathways:** Aimed at restoring parasympathetic dominance (the "rest and digest" state), thereby improving digestive secretions and coordinating gut motility.

- **Modulation of the neuro-immune response:** To reduce chronic local inflammation of the intestinal mucosa via the cholinergic anti-inflammatory pathway.
- **Re-coordination of gut motility:** By regulating the periodicity of the migrating motor complex (MMC), which cleanses the intestine and prevents gas-producing bacterial overgrowth (SIBO).

This physiological framework is the foundation upon which GastroZEN is designed as a peripheral neuromodulation tool. Rather than direct chemical intervention, the product aims to reflexively stimulate these three therapeutic axes via the cutaneo-visceral reflex pathway—a pathway whose physiological feasibility has been demonstrated in preliminary studies (Appendices 1 and 2), and which will be detailed in the next section.

3. Addressing Inflammatory Mechanisms in the Gut-Brain Axis

3.1. Physiological Basis: Why the Umbilical Region?

GastroZEN's design relies on a well-established physiological principle in neurophysiology: the cutaneo-visceral reflex. This principle states that stimulation of sensory nerves in the skin can evoke measurable reflex responses in internal organs via pathways that travel from the spinal cord to the brainstem. This is the same pathway whose central importance in targeting the vagus nerve and restoring autonomic balance was highlighted in earlier sections (1.2 and 2.4).

The periumbilical region was selected as the application site for this stimulation for the following anatomical reasons:

- **Segmental innervation:** The umbilical skin is sensibly innervated by the T10 spinal nerve. While the stomach and small intestine are innervated by the vagus and splanchnic nerves, the convergence of these two systems (sensory and visceral) occurs centrally in the spinal cord and brainstem. This neural convergence provides the anatomical substrate for cutaneo-visceral reflexes, allowing local T10 stimulation to influence the motor and secretory functions of internal organs.
- **High density of nerve endings:** The umbilical region is rich in free sensory nerve endings, providing a broad "sensing surface" for local chemical stimuli.
- **Ascending pathway:** Sensory signals generated in the umbilical skin travel via Aδ and C sensory fibers to the dorsal horn of the T10 spinal cord. From there, they ascend via sensory pathways to the nucleus tractus solitarius (NTS) in the brainstem, the first central relay for visceral sensory processing. From the NTS, signals are distributed to autonomic nuclei responsible for inhibiting the sympathetic system and activating the parasympathetic system (such as the dorsal motor nucleus of the vagus, DMV).

This anatomical pathway makes the umbilical region an ideal leverage point for modulating autonomic balance via a precise reflex arc, without requiring systemic absorption of the active ingredients.

3.2. Selection Criteria of Plant Extracts and Their Functional Role

GastroZEN's formulation comprises 12 aqueous plant extracts (hydrosols, isolates, distillates) selected according to a precise physiological criterion: the ability to selectively interact with sensory receptors in the dermis, without necessarily entering the systemic circulation. The water-based formulation, aided by hydration of the stratum corneum, facilitates limited local penetration sufficient to reach and interact with free nerve endings in the upper dermis, thereby triggering the reflex pathway without the need for systemic absorption. The active compounds in these extracts fall into four main chemical classes, each with a specific role in the reflex pathway:

- **Alkaloids:** Such as those found in Erythrina mulungu. They interact with peripheral GABA-A receptors on sensory nerve endings to modulate their excitability and reduce excessive sympathetic signaling.
- **Terpenes:** Such as those found in white guava and quinine. They act as selective activators of TRP channels (e.g., TRPV1, TRPA1), which are the primary receptors responsible for cutaneous chemical sensation.
- **Flavonoids:** Such as those found in Maytenus ilicifolia (Espinheira Santa) and Hymenaea courbaril (Jatobá). They possess local antioxidant and anti-inflammatory properties, preventing distortion of sensory signals caused by local neurogenic inflammation.
- **Phenolics**: Such as the extract of white Jatobá. They help protect the integrity of nerve endings from local oxidative stress.

In summary, each component was chosen not for its systemic action, but for its specific role in the cutaneo-visceral reflex pathway: either as a signal trigger, an excitability modulator, or a neural environment stabilizer.

3.3. Mechanism of Action: The Cutaneo-Visceral Reflex Pathway

Cutaneovisceral Reflex GastroZEN's mechanism of action relies on stimulating the cutaneo-visceral reflex, a well-established physiological pathway that allows reflex modulation of internal organ functions via neural routes without requiring active ingredients to reach the systemic circulation. The activation of this pathway was objectively verified in the proof-of-concept study (Appendix 2), where the vagal tone index (HF-HRV) increased by 20-35% within 30 minutes of application—a response that cannot be explained by any non-reflex mechanism.

Foundation on External Neuromodulation Principles: The Bridge Between Chemical Stimulation and Acupuncture

To understand this mechanism, it is useful to view GastroZEN not as a conventional lotion but as a topical neuromodulation tool based on the same physiological concept validated by modern acupuncture techniques. The common principle is that stimulating specific points on the body surface (somatotopic stimulation) produces measurable changes in internal organ function via central reflex pathways. While acupuncture uses a needle as a mechanical stimulus to generate a neural signal, GastroZEN uses active plant compounds as a selective chemical stimulus for the small sensory nerve fibers (Aδ and C) in the skin. Both approaches activate these fibers to transmit impulses to the central nervous system, eliciting a therapeutic visceromotor reflex response. This effect regulates digestive functions without skin penetration, providing a supportive, continuous method (through repeated application) for non-pharmacological transcutaneous vagus nerve stimulation.

The Process Follows These Sequential Steps:

- **Local Interaction (Cutaneous Reception):**

  GastroZEN's formulation provides pure plant compounds (such as quinine and terpenes) that act as selective chemical ligands for specialized sensory receptors in the dermis of the umbilical skin, specifically the TRP family of ion channels (e.g., TRPV1, TRPA1). These channels are physiologically responsible for translating chemical and thermal stimuli into neural language. When these compounds bind to TRP channels, the channel protein changes conformation, allowing an influx of positive ions (Ca^{2+} and Na^{+}) into the free nerve ending. This ionic flow generates a change in the cell membrane potential, producing an action potential—the fundamental electrical signal of the nervous system. This electrical impulse travels via Aδ and C sensory nerve fibers toward the spinal cord. This molecular-neural interaction is confined

to the dermal layer and does not reach the systemic circulation, as the water-based formulation facilitates the targeted delivery of these low-molecular-weight compounds specifically to these superficial receptors, converting the chemical energy of the plant extract into an electrical signal that triggers the reflex pathway.

– **Central Processing (Sensory-Autonomic Convergence):**

The generated cutaneous signals reach the T10 dorsal horn, where they converge anatomically and functionally with visceral inputs from digestive organs to form the neural substrate for cutaneo-visceral reflexes. Ascending via indirect, polysynaptic pathways—most notably the reticulospinal tract—these impulses bypass direct vagal pathways to target higher integrative centers such as the reticular formation and periaqueductal gray (PAG) for systemic autonomic processing.

– **Reflex Response (Reflex Vagal Modulation):**

From the reticular formation and PAG, direct projections descend to the main vagal nuclei in the medulla oblongata: the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMV). This reflex activation is thought to yield a dual response consistent with known neurophysiology:

- **Sympathetic withdrawal** via descending inhibitory pathways.
- **Parasympathetic activation** via increased efferent output from the DMV to the viscera.

Through this indirect mechanism, cutaneous stimulation at the T10 dermatome is translated into selective enhancement of vagal activity, without assuming a direct anatomical pathway that does not exist.

– **Integrated Functional Effect (Return to "Rest and Digest"):**

This autonomic shift toward parasympathetic dominance primes the gastrointestinal tract to re-enter the "rest and digest" state. Clinically, this translates into independent yet interconnected effects observed in preliminary follow-ups, including: restoration of migrating motor complex (MMC) periodicity (improving cleansing motility), coordination of digestive secretions (acid, enzymes, mucus), and reduction of local inflammation via activation of the cholinergic anti-inflammatory pathway.

Bridging the Gap Between Local Stimulus and Systemic Response: The Neural Amplification Model

A logical physiological question arises: How can a small-area topical chemical stimulus produces a profound systemic shift in autonomic balance, especially given that the resulting sensory signal does not exceed the threshold for strong pain or intense sensation? The answer lies in understanding the pathophysiology of functional disorders, specifically the concepts of central sensitization and sensory gating deficiency. In IBS and disorders associated with sympathetic overactivity, the patient's central nervous system is in a state of hyperexcitability. This means cutaneous sensory receptors (e.g., TRP channels) are hypersensitive, and sensory gating mechanisms at the spinal and brainstem levels are dysfunctional—weak signals are amplified rather than filtered out.

In this context, GastroZEN's regular stimulus (3 times daily on the T10 dermatome) acts as a sub-threshold signal in a healthy person but becomes supra-threshold in the hyperexcitable CNS of the functional disorder patient. This phenomenon can be explained by the principle of stochastic

resonance in biological systems: a weak, regular, periodic signal added to a system with high "internal noise" helps it overcome a certain dynamic threshold, pushing it from a state of instability (irregular MMC, pain) to a state of stability (parasympathetic dominance). This selective amplification allows a non-invasive local stimulus to produce a profound autonomic shift with cumulative clinical effect. In other words, this mechanism does not assume the product is exceptionally "strong"; rather, it assumes it is precise and regular enough to exploit the patient's neural hypersensitivity for their benefit, restoring lost balance.

The complete details of this mechanism, including the three-stage functional model of the components, are presented in section 3.4.

3.4. The Functional Integration Model: A Three-Stage Mechanism

GastroZEN's components work integrally across three functional stages—whose physiological effects have been verified in preliminary studies (Appendices 1 and 2)—targeting the cutaneo-visceral reflex pathway from start (skin) to finish (vagus nerve).

Functional Stage	Primary Components	Supporting Components	Mechanism of Action for the Group	Physiological Basis
1. Sensory Tissue Priming (Normalizing the Cutaneous Neural Environment)	Erythrina mulungu (alkaloids)	Trichilia catigua (Catuaba), Ptychopetalum olacoides (Marapuama)	Alkaloids & Catuaba/Marapuama: Act as potent antioxidants and local cytokine inhibitors, reducing mild neural inflammation and oxidative stress on cutaneous sensory endings.	Peripheral neural inflammation raises the stimulation threshold and distorts sensory signals. Normalizing the skin's microbial and chemical environment improves the signal-to-noise ratio for the next stage.
2. Selective Sensory Stimulation (Generating the Reflex Signal)	Cinchona sp. (Quinine), Psidium guajava (Amazonian White Guava Isolate)	Myrcia amazonica (Pedra Hume Caá), Bauhinia sp. (Pata de Vaca)	Quinine & White Guava: Selective activators of TRPV1/TRPA1 ion channels in the umbilical dermis, generating a robust, physiologically-defined sensory signal transmitted via Aδ/C afferents to the T10 dorsal horn. Pedra Hume Caá & Pata de Vaca: Hydrating antioxidants that protect nerve ending integrity during repeated stimulation.	TRP channels are the primary molecular gateway for cutaneous chemical sensation. Their activation reliably triggers the cutaneo- reflex, feeding the brainstem centers with the required signal.

Functional Stage	Primary Components	Supporting Components	Mechanism of Action for the Group	Physiological Basis
3. Reflex Response Guidance & Protection (Stabilizing the Vagal Effect and Preventing Distortion)	Maytenus ilicifolia (Espinheira Santa), Hymenaea courbaril (Jatobá)	Carapa guianensis (Andiroba), Dipteryx odorata (Cumaru), Cayaponia tayuya (Tayuya)	Espinheira Santa & Jatobá: Targeted neuro-antioxidants and anti-inflammatories, limiting local neurogenic inflammation from repeated stimulation, preserving signal fidelity with continued use. Andiroba, Cumaru, Tayuya: Provide additional antioxidant support and skin repair; believed to contribute to reflex sympathetic response stability via indirect pathways.	Local neural inflammation and oxidative stress weaken reflex pathway efficiency over time. Inhibiting these processes maintains the sustainability of the effect.

3.5. Differentiation from Conventional Approaches

Approach	Mechanism of Action	Scope of Effect	Documented Significant Risks
PPIs	Inhibits proton pump enzyme	Secretory only	– **Common:** Mg deficiency (43%), B12 deficiency (65%), SIBO (71%), drug dependence, difficult weaning (44%). – **Serious (rare):** CKD, dementia (use >4.4 years), cardiovascular disease, C. diff infection.
Antacids	Chemical pH modification	Local, temporary	– **Common:** Constipation (Al salts), diarrhea (Mg salts), metabolic alkalosis. – **Serious (rare):** Kidney stones (chronic Ca salts), Al accumulation (dementia), milk-alkali syndrome.
Prokinetics	Dopamine/serotonin receptor activation	Limited motility	– **Common:** Drowsiness, diarrhea, extrapyramidal symptoms (metoclopramide). – **Serious (rare):** Tardive dyskinesia (metoclopramide), ventricular arrhythmias/sudden death (domperidone).
Antispasmodics	Smooth muscle relaxation	Limited motility	– **Common:** Dry mouth, blurred vision, constipation, urinary retention (anticholinergic). – **Serious (rare):** May mask bowel obstruction or esophagitis.
Librax	Chemical neural inhibition: benzodiazepine + anticholinergic	Dual: psychiatric (anxiolysis) + motor (cramp relief)	– **Common:** Sedation, dependence, temporary cognitive impairment. – **Serious (rare):** Suicidal ideation/behavior, life-threatening withdrawal (seizures, psychosis), death risk when mixed with alcohol/opioids.

Approach	Mechanism of Action	Scope of Effect	Documented Significant Risks
GastroZEN	Peripheral neuromodulation via vagus nerve	Integrated (secretory, motor, immune, psychiatric)	– **Common:** No systemic risks reported. Very rare, temporary local reactions (redness, mild sensitivity). – **Serious (rare):** None reported to date.

4. Specified Clinical Applications

4.1. Irritable Bowel Syndrome (IBS)

Pathological Context:

IBS is among the most common functional gastrointestinal disorders. Patients exhibit variable symptoms across constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), or mixed (IBS-M) patterns, along with recurrent abdominal pain and chronic bloating. As detailed in sections 1.2 and 2.4, **this disorder is attributed to gut-brain axis dysfunction manifesting as:**

- Low baseline parasympathetic activity, which weakens the migrating motor complex (MMC) and leads to retained food and bacteria in the small intestine.
- Visceral hypersensitivity, where the neural pain threshold is lowered and normal physiological stimuli are interpreted as pain signals.
- Psychomotor reactivity, where chronic stress exacerbates intestinal spasms.

Clinical Observations from the Practice Record:

Based on the documented observation record (over 300 patients), the following response pattern was observed in IBS patients:

- **Days 3–5:** Initial improvement in pain intensity and cramps in the majority of patients (50–70%), with audible bowel sounds (borborygmi, a sign of returning MMC) in 71% of users.
- **Days 7–9:** Improvement in the regularity of bowel patterns (both constipation and diarrhea) alongside improved parasympathetic activity measured by HRV—an improvement paralleling that objectively confirmed in the proof-of-concept study (Appendix 2, where HF-HRV increased by 20-35%).
- **Days 11–26:** Symptom stabilization with reduced bloating, and sustained improvement upon completing the protocol.

Clinical Positioning:

GastroZEN is proposed as an investigative tool for physicians to evaluate in refractory functional cases that have not responded adequately to conventional treatments. This proposal is based on a physiological model targeting restoration of autonomic neural balance, aligning with the modern understanding of the vagus nerve's role in functional gastrointestinal disorders (see section 2.4). The final decision regarding use remains subject to the treating physician's judgment, based on individual patient response and the complete clinical profile.

4.2. Functional Dyspepsia & GERD

Pathological Context:

Patients with functional dyspepsia experience symptoms of early satiety, postprandial fullness, upper dyspepsia, and nausea without any apparent organic pathology. This disorder often overlaps with gastroesophageal reflux disease (GERD), especially when reflux results from functional weakness of the lower esophageal sphincter (LES) rather than from acid hypersecretion.

As detailed in section 2.4.2, weak parasympathetic signaling plays a pivotal role in this condition, as the vagus nerve loses its ability to efficiently coordinate acid secretion and valve closure.

Clinical Observations from the Practice Record:
Based on the documented observation record, the following response pattern was observed:

- **Improved gastric emptying:** Patients reported improvement in early satiety and nausea within 4-7 days.
- **LES closure support:** In GERD cases associated with valve weakness, improvement in reflux symptoms was observed within one to two weeks, especially when combined with magnesium repletion.
- **Shift away from PPIs (for users of less than 3 months):** 65% of patients who had been using PPIs for no more than 3 months, and who discontinued PPIs before starting GastroZEN, have not needed to return to PPIs to date.

Proposed Intervention Mechanism of GastroZEN:
It is proposed that GastroZEN, via the cutaneo-visceral reflex mechanism (section 3.3), contributes to:

- **Restoring secretory balance:** By activating parasympathetic pathways—an effect objectively documented in our preliminary studies via increased vagal tone (HF-HRV) in Appendix 2—thereby supporting coordinated secretion of acid, mucus, and enzymes without chemical inhibition.
- **Supporting LES closure:** By restoring appropriate physiological acidity and activating the neuro-hormonal signals responsible for increasing sphincter pressure.
- **Supporting mucosal protection:** It contributes to enhanced mucus production (thanks to the Espinheira Santa content), which may provide additional mucosal protection, a matter of particular importance for patients with a history of PPI use.

Clinical Positioning:
GastroZEN is proposed as an investigative tool for physicians to evaluate in:

- Functional dyspepsia that has not responded adequately to conventional prokinetics.
- Cases of functional GERD due to valve weakness (LES): It is used only for patients who used PPIs for less than 90 days and discontinued them before starting GastroZEN. For those who have exceeded 90 days of continuous use, the rehabilitation protocol in section 4.2.1 must be reviewed first.
- Cases where the physician seeks to support mucosal health in patients who have discontinued PPIs (after a use period of less than 90 days), while monitoring response. GastroZEN is not used as a weaning tool from PPIs; the process of discontinuing PPIs must be carried out separately and under medical supervision, according to the appropriate protocol.

4.2.1. The Chronic PPI Conundrum: Why Might a Patient Not Respond to GastroZEN Alone?

Clinical Context:
Based on clinical observations, it has been noted that patient responses to GastroZEN may vary according to their prior duration of PPI use. In particular, patients who have used PPIs for more than 3 months may not achieve the expected physiological response with GastroZEN alone. This challenge is attributed to a set of documented adaptive changes induced by prolonged acid suppression in the gastrointestinal tract and nervous system.

Physiological Changes After Prolonged PPI Use (+3 months):

- Parietal cell adaptation (paracrine adaptation): The acid-producing cells of the stomach reprogram their function to depend on the presence of the suppressive drug. Upon abrupt discontinuation, rebound acid hypersecretion occurs, which may last 2–4 weeks, temporarily exacerbating symptoms and hindering any intervention that does not target cellular restructuring.
- Chronic TRPM6/7 channel dysfunction: Long-term PPI use is associated with structural magnesium ion deficiency. This deficiency negatively affects lower esophageal sphincter (LES) function and neuromuscular plasticity, perpetuating the state of functional reflux even after the causative drug is discontinued.
- Reversed central neural reprogramming: The chronic absence of the acid signal leads the brainstem neural centers to habituate to this absence. The result is a weakened natural vagal reflex response when acidity is restored, requiring time to reset these pathways.

Physiological Challenge:

GastroZEN's proposed mechanism (section 3.3) aims to reset neural signals via vagus activation. However, it does not rebuild the altered cellular and chemical "infrastructure." Therefore, a patient with this history of prolonged use may require a preparatory rehabilitation protocol to restore the physiological environment before being able to benefit from neuromodulation.

Conclusion for the Physician: Clinical observations suggest that patients with a history of PPI use exceeding 3 months may need a sequential approach that begins with a preparatory rehabilitation phase (e.g., gradual dose tapering and supportive measures determined by the physician) before using GastroZEN. Accordingly, GastroZEN is not proposed as an immediate substitute for this category of patients without undergoing this preparatory phase. The final decision regarding the details and duration of the protocol remains subject to the treating physician's judgment.

4.3. Helicobacter pylori (H. pylori)

Pathological Context:

H. pylori infection is among the most common infections worldwide, but its presence does not necessarily imply disease; a large proportion of carriers remain completely asymptomatic throughout their lives. The difference between "silent carriage" and "active disease" lies in the host environment: mucosal barrier integrity, neuro-immune balance, and blood perfusion efficiency. As detailed in section 2.4.3, the vagus nerve plays a pivotal role in regulating these defenses.
Dysregulation

- **Impaired gastric environment:** Weak parasympathetic activity deprives the gastric mucosa of its natural protection (mucus, bicarbonate, perfusion), transforming bacterial presence into a pathogenic factor.
- **Inflammatory neural programming:** Persistent local inflammation establishes a vicious cycle of pain and bloating; this programming may persist even after the bacterium has been eradicated with antibiotics.
- **Exaggerated immune response:** Sympathetic hyperactivity keeps neuro-inflammatory pathways on high alert, increasing mucosal sensitivity.

Proposed Intervention Mechanism of GastroZEN:

It is proposed that GastroZEN, via the cutaneo-visceral reflex mechanism (section 3.3), does not target the bacterium directly but rather helps modulate the host environment that the bacterium requires to cause damage, through:

- **Restoring the mucosal barrier:** By enhancing vagal signals, which may support activation of protective mucus and bicarbonate secretion and improve mucosal perfusion.
- **Resetting neuro-immune regulation:** Via the cholinergic anti-inflammatory pathway, GastroZEN is thought to help calm the chronic inflammation cycle that makes bacterial presence pathogenic.
- **Breaking pathological neural programming:** Terminating the "inflammatory memory" of the enteric nervous system may help reduce pain and visceral hypersensitivity associated with bacterial presence.
- **Proposed physiological outcome:** The mucosa transitions from a fragile, inflamed state to a more balanced, stable environment—potentially not conducive to provoking bacterial symptoms, similar to the state of millions of asymptomatic carriers.

Clinical Positioning:

GastroZEN is proposed as an investigative tool for modulating the host environment in cases where functional symptoms (pain, bloating, dyspepsia) are associated with H. pylori presence. It is important to emphasize that GastroZEN does not replace triple/quadruple therapy if there is a medical indication for eradication. The physician may evaluate its use in the following scenarios:

- As a tool for mucosal rehabilitation and inhibiting the bacterium's ability to cause damage.
- As an investigative option for patients with symptoms and confirmed H. pylori who do not wish to immediately undergo antibiotic protocols.
- As a supportive recovery tool after pharmacological eradication for patients whose functional symptoms persist despite successful antibiotic treatment.

4.4. Accompanying Psychological Expressions of Gut-Brain Axis Disorders (Gut-Directed Anxiety)

Pathological Context:

In clinical practice, it is observed that a significant proportion of patients with functional gastrointestinal disorders suffer from accompanying psychological expressions, ranging from gut-directed anxiety and mild depression to sleep disturbances. In some cases, this anxiety may escalate to episodes of acute, unprovoked fear, intensifying the daily burden of suffering. As detailed in sections 2.2 and 2.4.4, these symptoms are not merely a "reaction" to pain but are part of the integrated dysfunction of the gut-brain axis, where weak vagal signals lead to hyperactivity of the HPA axis (stress axis).

Dysregulation

- Disruption of bidirectional communication between the enteric plexus and the brain regions responsible for fear processing (amygdala, hippocampus).
- Hyperactivity of the HPA axis associated with chronic stress.
- Reduced spinal inhibitory signals for visceral pain, thereby increasing the sensation of discomfort.

Proposed Intervention Mechanism of GastroZEN:

It is proposed that GastroZEN, via the cutaneo-visceral reflex mechanism (section 3.3) and activation of ascending cholinergic pathways (section 2.5), may contribute to:

- **Alleviating gut-directed anxiety:** By enhancing parasympathetic activity, which may help inhibit amygdala activity and the fear response associated with gastrointestinal symptoms.
- **Improving sleep quality:** The observation record noted improved sleep quality in some users, and it is hypothesized that this may be related to inhibition of the excessive sympathetic response responsible for insomnia.
- **Breaking the vicious cycle:** By improving physical symptoms (sections 4.1 and 4.2), which may help reduce associated anxiety, thereby improving the overall sense of well-being.

Clinical Recommendation:

GastroZEN is proposed as an investigative tool for physicians to evaluate in cases where psychological and physical symptoms overlap, especially in the following scenarios:

- When anxiety regarding gastrointestinal symptoms is a major aggravating factor of the condition.
- When purely psychological-behavioral or pharmacological approaches do not achieve adequate improvement on their own.
- When the patient prefers a non-pharmacological option that can be used as a complementary investigative tool within the treatment plan.

5. Therapeutic Protocol & Stages of Neural Reprogramming

5.1. Guiding Principles of the Protocol

The proposed framework for GastroZEN use is based on two key observations from the practice record: first, that initial improvement may be noticeable within the first few days; second, that continuity of application is essential to prevent symptom return. This aligns logically with the physiological mechanism supported by preliminary data (Appendices 1 and 2), which confirms that restoring autonomic neural balance requires repeated, regular stimulation of the reflex pathway (section 3.3). Accordingly, use is organized into three progressive time phases, with monitoring of clinical response.

5.1.1. Stage One: Initial Improvement & Early Response (Days 3–5)

Goal: Initiate calming of the excessive sympathetic response and activation of parasympathetic pathways.

Application Method:

Apply the lotion to the periumbilical region (shave hair if present) in sufficient quantity to cover the area with a thin layer, with gentle massage for 30–60 seconds. Repeat application 3 times daily (morning, noon, evening).

Observed Clinical Indicators (from the practice record):

- Reduction in the severity of visceral pain and intestinal cramps.
- Improvement in overall abdominal comfort.
- Beginning of sleep pattern regulation in some patients.
- Audible bowel sounds (borborygmi) in 71% of users, considered an early positive sign of returning MMC function.

- Marked improvement in symptom severity observed in the majority of patients during this stage.

Considerations:

The speed of initial response varies according to patient age, disease duration, and previously used medications. Patients with a long history of PPI use (more than 3 months) may show slower, more gradual improvement (see section 4.2.1).

5.1.2. Stage Two: Sustained Improvement & Functional Recovery (Days 7–9)

Goal: Continued symptom improvement with beginning stabilization of bowel pattern and digestive functions.

Observed Clinical Indicators (from the practice record):

- Gradual stabilization of bowel pattern and reduced postprandial bloating.
- Diminishing heartburn and reflux in functional GERD cases associated with LES weakness.
- Improved appetite and ability to complete meals without early satiety.

5.1.3. Stage Three: Functional Stability & Reduced Relapse Probability (Days 11–26)

Goal: Continued use to contribute to stabilization of autonomic balance and prevention of symptom return.

Application Method:

Continue application 3 times daily until the contents of the bottle (50 mL) are exhausted, which provides approximately one month of use with adherence.

Observed Clinical Indicators (from the practice record):

- Improved regularity of MMC and reduced symptoms of bacterial overgrowth (SIBO).
- Reduced sensitivity to dietary and psychological triggers.
- Restoration of ionic balance (especially magnesium) in patients who discontinued acid suppressants.
- Completing the full bottle contributes to reduced probability of symptom return.

Clinical Rationale:

Completing the recommended 4-week course is thought to allow the reflex pathway sufficient time to reach a state of functional stability, potentially reducing the likelihood of symptom relapse.

5.2. Clinical Application Criteria & Precautions

Application area:
The umbilical and periumbilical area (5 cm radius). Apply the lotion to clean, dry skin.

Dosage & Frequency:

- **Dose:** Amount sufficient for a thin, uniform layer (approximately 0.5–0.7 mL).
- **Frequency:** 3 times daily (morning, noon, evening).
- **Duration:** Until the bottle is exhausted (50 mL, approximately one month of regular use).

Mandatory Precautions:

- Do not use on open wounds or irritated skin.
- Avoid contact with eyes and mucous membranes.
- Wash hands after application.
- Insufficient data on use during pregnancy, lactation, or in dialysis patients; therefore, use with caution under the treating physician's judgment.

5.3. Follow-up Criteria & Stop Signs

Recommended Follow-up:

- Initial assessment after 4 days of use (to verify initial response).
- Second assessment after one week (to evaluate sustained improvement).
- Final assessment after bottle exhaustion (to evaluate durability of response).

Red Flags Requiring Conventional Investigation:

Red Flags Requiring Conventional Investigation:

- Unexplained weight loss.
- Hematemesis or melena (black, tarry stools).
- Progressive dysphagia (difficulty swallowing).
- Anemia accompanied by gastrointestinal symptoms.
- Persistent abdominal pain unrelated to meals.

5.4. Individual Expectations & Factors of Variability

Individual Expectations & Factors of Variability

Factor	Impact on Response
Prolonged PPI history	Improvement may be slower due to ionic dysregulation and the period of chronic dependence (see section 4.2.1).
Severe chronic stress	May require a longer time for autonomic balance to shift toward parasympathetic dominance.
Disease duration	Chronic disorders (more than 5 years) may benefit from a second treatment cycle.
Application adherence	Irregularity may weaken the observed effect, as repeated stimulation of the reflex pathway is necessary to achieve functional stability.

Summary:

Clinical observations indicate that early improvement within the initial days—while a positive indicator—does not necessarily imply the complete restoration of functional homeostasis. It is suggested that completing the recommended 4-week course of application may facilitate long-term stability. The final determination regarding the duration of use and the necessity of additional cycles remains at the discretion of the attending physician, based on the patient's individual clinical response

6. Safety, Interactions, and Clinical Considerations

6.1. General Safety Profile

Available safety data for GastroZEN are based on:

- The traditional history of safe use of its botanical components in Brazilian and South American medical practices.
- Limited clinical studies on individual extracts (Mulungu, Espinheira Santa, Jatobá).

– Patient anecdotal reports in informal settings (Post-marketing Surveillance).

Clinical Profile Summary:

No serious systemic adverse events attributable to GastroZEN have been recorded in the available usage data. Localized reactions—when they occur—are reported as very rare and transient, including:

Localized Reaction	Frequency	Clinical Description	Management
Mild warming sensation	Very rare	Transient; occurs upon initial application.	Reduce application frequency to twice daily (12-hour intervals) to allow for a skin recovery period.
Slight cutaneous numbness	Very rare	Transient localized sensation at the site of application.	Reduce application frequency to twice daily (12-hour intervals).
Localized erythema	Rare	Mild, localized skin discoloration.	Reduce application frequency to twice daily (12-hour intervals).
Cutaneous hypersensitivity	Very rare	Occurs in individuals with hypersensitive skin to medicinal herbs.	Discontinue use immediately.

Clinical Recommendation: In the event of any abnormal response or persistent discomfort, immediate discontinuation of use is advised, along with consultation with a qualified physician.

6.1.1. Additional Note on Potential Non-Localized Effects

In the clinical observation registry, a limited percentage of female users reported alterations in menstrual patterns (specifically, a reduction in menstrual flow volume or duration). This observation is not understood to be a direct hormonal adverse effect; rather, it can be conceptualized as a systemic "allostatic adjustment." Physiologically, a significant shift toward parasympathetic dominance leads to acute suppression of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a substantial decline in cortisol levels. This abrupt reduction in cortisol may indirectly enhance the stability and regularity of the hypothalamus-pituitary-gonadal (HPG) axis by removing the inhibitory effect that cortisol typically exerts on this pathway. Consequently, the menstrual cycle returns to a more regular, less profuse physiological "baseline," representing a corrective shift rather than a harmful adverse effect. This effect—if present—is believed to be transient and associated with the body's self-regulatory reset period (allostasis).

Caution: Given that the exact mechanism of this observation is not fully elucidated, it is recommended to inform female patients prior to initiating use, document any changes in menstrual patterns, and discontinue use if there is clinical concern or a desire for pregnancy

6.2. Anticipated Physiological Effect: Parasympathetic-Induced Hypotension

Since the mechanism of action of GastroZEN aims to enhance parasympathetic tone—an effect objectively demonstrated in the data of Appendix 2—a slight decrease in blood pressure is physiologically anticipated due to parasympathetic-mediated vasodilation. This potential effect warrants clinical monitoring in the following populations:

– Patients with hypotension.

- Patients taking antihypertensive medications.
- The elderly.

6.3. Potential Drug Interactions

Drug Class	Interaction Mechanism	Clinical Recommendation
Proton Pump Inhibitors (PPIs)	No known direct drug-drug interaction.	Based on the product's physiological hypothesis, symptom improvement may allow for a gradual tapering of the PPI dose. This must be conducted under strict medical supervision to monitor for rebound acid hypersecretion.
Prokinetics	Potential additive effect on enhancing gastrointestinal motility.	Caution is advised to avoid gastrointestinal hypermotility (e.g., diarrhea or abdominal cramping).
Antihypertensive Medications	Parasympathetic activation may potentiate the blood pressure-lowering effect.	Clinical data are insufficient. Use with caution and monitor blood pressure, particularly during the initial phase of administration.
Anxiolytics / Hypnotics (Benzodiazepines)	Potential theoretical interaction via GABA-A receptors with *Mulungu* alkaloids.	Caution is advised; an additive sedative effect may occur, which might necessitate Benzodiazepine dosage adjustment under medical supervision.
Anticoagulants / Antiplatelets (Warfarin, Antiplatelets)	Potential theoretical effect of certain flavonoids on blood coagulation.	Clinical data are insufficient. Use with caution; monitoring of the Prothrombin Time / International Normalized Ratio (PT/INR) is advised for patients on Warfarin.

6.4. Contraindications and Warnings

Absolute Contraindications:

- Open wounds, burns, or areas of compromised skin integrity.
- Active dermatological diseases or localized skin infections at the site of application.
- Confirmed hypersensitivity to any of the botanical ingredients listed on the packaging.

Warnings and Precautions:

- **General Safety:** Apply strictly to intact skin; avoid application to open wounds or irritated dermal layers, and exercise extreme caution to prevent contact with the eyes.
- **Pregnancy:** Although no negative adverse effects have been reported during use, due to the lack of sufficient clinical safety studies during gestation, consultation with a physician or use under strict medical supervision is recommended as a precautionary measure.
- **Lactation:** The product is considered safe for use during breastfeeding, and no negative adverse effects have been recorded to date.
- **Dialysis Patients:** Clinical data are insufficient; use with extreme caution under close medical supervision.
- **Patients on Antihypertensive Therapy:** Routine blood pressure monitoring is advised, as a mild additive hypotensive effect may occur with concurrent use in some cases.

6.5. Special Considerations for Prolonged Use

Although the recommended treatment window spans one month (completion of one bottle), certain patients may require repeated cycles or seasonal administration. In these cases:

- No pharmacological tolerance or physical dependence has been observed in available clinical data.
- A 1–2week washout period is recommended between consecutive cycles if the product is used continuously for more than 3 months.
- Clinical re-evaluation every 3 months is advised to confirm the ongoing medical necessity of treatment.

6.6. Adverse Event Reporting

Due to the product's classification as a botanical formulation, spontaneous adverse event reporting remains limited. Physicians are strongly encouraged to document and report.

- Any unexpected dermatological or cutaneous reactions.
- Shifts in baseline blood pressure or heart rate.
- Any suspected drug-herb interactions.

7. Clinical Recommendations and Prescription Methodology

7.1. Patient Selection Criteria

GastroZEN is presented as an investigative tool for physicians to evaluate in patients sharing common clinical profiles. It is unlikely to be effective in purely organic cases requiring surgical intervention or high-intensity pharmacological treatment. Evaluation of its use may be considered when the following criteria are met:

Inclusion Criteria (Potential Responder Profiles):

- Diagnosis of a functional gastrointestinal disorder (IBS, functional dyspepsia, functional GERD) according to Rome IV criteria or differential clinical assessment.
- Persistence of symptoms despite optimized use of conventional treatments.
- Indirect indicators of brain-gut axis dysfunction (accompanying anxiety, insomnia, symptoms worsening with stress, or heart rate variability (HRV) disturbance if available).
- Patient's ability to adhere to a regular application protocol for a duration of 4 weeks.

7.2. Role of GastroZEN in the Therapeutic Strategy: Stimulating Self-Recovery

The proposed mechanism of GastroZEN differs from pharmacological approaches that target the suppression of a single symptom. Based on its physiological model and preliminary data (Appendices 1 and 2), it is suggested that it works indirectly by modulating autonomic nervous system activity toward a parasympathetic state (Section 3.3). Based on clinical observations and these physiological data, physicians can evaluate its use in the following contexts:

- **Functional Disorders (IBS, Functional Dyspepsia, Functional GERD):** Proposed as an investigative option to support the restoration of autonomic balance in the digestive system, which may positively affect motility, secretions, and local immunity, especially in cases non-responsive to standard treatments.
- **Helicobacter pylori (H. pylori) Cases:** Presented as a tool to modify the host environment by supporting mucosal barrier restoration and modulating neuro-inflammatory responses. This approach does not target the bacteria directly but aims to make the environment less conducive to damage (see Section 4.3).

- **Supporting PPI De-escalation:** For patients using Proton Pump Inhibitors (PPIs) for less than 3 months (according to the protocol in Section 4.2), GastroZEN can be evaluated as a tool to support the restoration of secretory and motor functions after discontinuing PPIs.

7.3. Usage Instructions for the Patient

- **Application:** Apply a thin layer of the lotion to the umbilicus and the surrounding umbilical region (5 cm) after cleaning and drying the skin.
- **Frequency**: 3 times daily (morning, noon, evening).
- **Movement:** Light circular motion for 30–60 seconds in a clockwise direction.
- **Duration:** Continue until the bottle is finished (50 ml, which is approximately sufficient for one month of regular use), even if early improvement in symptoms is noted.
- **Follow-up:** It is suggested to see a doctor after one week to evaluate the initial response, and again when the bottle is finished to evaluate the sustainability of the response.

Supportive Recommendations:

- Maintain a balanced diet and avoid known irritants (heavy fats, excessive caffeine, alcohol) during the period of use.
- Maintain a daily Symptom Diary to facilitate objective assessment of the response.

7.4. Assessment and Follow-Up Criteria

- **Week 1 (Early Assessment):** The following metrics may be utilized:
  - Abdominal pain severity (Visual Analog Scale [VAS] 0–10).
  - Frequency of diarrhea/constipation.
  - Degree of abdominal distension/bloating.
  - Sleep quality.
  - Concomitant anxiety level (abbreviated GAD-7).
- **Completion of Treatment Course (Final Evaluation):** The Gastrointestinal Symptom Rating Scale (GSRS) or any available simplified metric may be used. Improvement in comorbid anxiety and depression, if present, should also be assessed
- **Determination of Treatment Extension:** If a sustained improvement of ≥ 75% is achieved, a 2–4week washout period may be recommended. If the improvement is partial (50–75%), evaluating the patient for a second treatment cycle may be beneficial**.**

7.5. Managing Clinical Expectations

Clear communication with the patient is vital to align expectations. The physician may clarify the following points:

- Noticeable clinical improvement may occur within 4–7 days; however, completing the full course is advised to achieve long-term functional stability.
- The product is not indicated for the treatment of severe organic pathology (e.g., bleeding ulcers, malignancies, obstructions).
- Inter-individual variability in clinical response is normal and anticipated, correlating with the patient's medical history and prior pharmacological interventions.

8. Overall Clinical Conclusion

GastroZEN is presented as an emerging therapeutic option backed by robust preliminary evidence, aiming to restore the functional homeostasis of the gut-brain axis via a cutaneovisceral reflex mechanism and vagal nerve activation. This proposition is based on:

- **A Physiological Model:** Linking parasympathetic hypoactivity to functional gastrointestinal disorders (Sections 1.2 and 1.3).
- **A Clinical Observation Registry:** Encompassing over 300 patients who demonstrated significant symptomatic improvement in irritable bowel syndrome (IBS), functional dyspepsia, and reflux associated with lower esophageal sphincter (LES) insufficiency.
- **A Randomized, Placebo-Controlled Proof-of-Concept Study (Appendix 2):** Demonstrating a 20–35% increase in vagal activity (HF-HRV), a more than twofold elevation in the visceral pain threshold, and the normalization of fecal calprotectin, with an effect size (Cohen's d > 2.0) that far exceeds the threshold for clinical significance.

Available observations indicate that symptomatic improvement may initiate within 4–7 days in the majority of patients, and that continuing application for 4 weeks may facilitate long-term functional stability.

Future Steps: These data strongly support the efficacy of this therapeutic approach. The company is currently planning to expand its documentation through multicenter clinical trials to validate these findings on a broader scale.

Current Clinical Positioning: Based on this evidence, GastroZEN is positioned as an investigative tool that physicians—at their professional discretion—may evaluate in refractory functional cases where standard therapeutic options have been exhausted.

9. References

1. Neurogastroenterology Mayer EA. Gut feelings: the emerging biology of gut–brain communication. Nature Reviews Neuroscience. 2011;12(8):453–466.
2. Gut–Brain Axis Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology. 2015;28(2):203–209.
3. Vagus Nerve Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Frontiers in Neuroscience. 2018;12:49.
4. Cholinergic Anti-inflammatory Pathway Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853–859.
5. Heart Rate Variability Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biological Psychology. 2007;74(2):224–242.
6. Irritable Bowel Syndrome Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. Gastroenterology. 2016.
7. Visceral Hypersensitivity Van Oudenhove L, Crowell MD, Drossman DA, et al. Biopsychosocial aspects of functional gastrointestinal disorders. Gastroenterology. 2016.
8. Cutaneo-Visceral Reflex Sato A, Sato Y, Schmidt RF. Reflex effects of somatic sensory stimulation on autonomic functions. Reviews of Physiology, Biochemistry and Pharmacology. 1997;130:1–328.
9. TRPV1 Receptors Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389(6653):816–824.
10. Central Sensitization Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–S15.
11. Stochastic Resonance McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. PLoS Computational Biology. 2009;5(5):e1000348.

12. Proton Pump Inhibitors Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice. Gastroenterology. 2017;152(4):706–715.
13. Migrating Motor Complex Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. Nature Reviews Gastroenterology & Hepatology. 2012;9(5):271–285.
14. Brain–Gut Interaction Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nature Reviews Gastroenterology & Hepatology. 2009;6(5):306–314.
15. Autonomic Nervous System Benarroch EE. The central autonomic network: functional organization and clinical correlations. Armonk Neurology. 1993;50(10):105–111.
16. Proton Pump Inhibitors Reimer C, Søndergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology. 2009;137(1):80–87.
17. Hypomagnesemia Hess MW, Hoenderop JGJ, Bindels RJM, Drenth JPH. Systematic review: hypomagnesaemia induced by proton pump inhibition. Alimentary Pharmacology & Therapeutics. 2012;36(5):405–413.
18. Small Intestinal Bacterial Overgrowth Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clinical Gastroenterology and Hepatology. 2010;8(6):504–508.
19. Lower Esophageal Sphincter Mittal RK, Balaban DH. The esophagogastric junction. New England Journal of Medicine. 1997;336(13):924–932.
20. Magnesium Transport Channels Schlingmann KP, Gudermann T. A critical role of TRPM channel-kinase for human magnesium transport. Journal of Physiology. 2005;566(Pt 2):301–308.
21. Vagal Tone Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Frontiers in Public Health. 2017;5:258.

Appendix

An Exploratory Physiological Study: Evaluating the Efficacy of Transcutaneous Neuromodulation in Restoring Gut-Brain Axis Homeostasis

Overview

This study investigates the physiological effects of the "GastroZEN" formulation as a peripheral neuromodulation system aimed at supporting the restoration of functional gastrointestinal homeostasis in cases of irritable bowel syndrome (IBS) and post-H. pylori infection states. The methodology relies on activating the cutaneo-visceral reflex arc to stimulate the vagus nerve and modulate the localized immune response. The results demonstrated substantial improvement in biomarkers over a 60-day follow-up period.

Methodology and Clinical Investigations

The research protocol was divided into two parallel investigative pathways designed to measure organic and neurological responses:

Table (1): Neuromodulation Indices and Gastrointestinal Dynamics

Physiological Investigation Type	Measured Metric	Observed Biological Impact
Spectral HRV Analysis	Vagal Tone (HF Band)	Restoration of parasympathetic dominance and suppression of pain-associated sympathetic hyperactivity.
Multichannel EGG (Electrogastrography)	Slow Wave Coherence	Transitioning gastric dysrhythmia into regular electrical entrainment.
Laser Doppler Flowmetry (LDF)	Mucosal Microcirculation	A 28% increase in microvascular perfusion, accelerating cellular metabolism.
Baroreflex Sensitivity	Autonomic Stability	Enhancing the body's capacity to manage systemic stress episodes and mitigating visceral hypersensitivity.

Post-Infection Recovery

This section focuses on the role of neuromodulation in repairing tissues damaged by H. pylori endotoxins (VacA & CagA).

Table (2): Metabolomic and Immunological Investigations for Tissue Repair

Investigative Pathway	Targeted Mechanism	Expected Laboratory Outcome
Microdialysis Analysis	Interstitial Cytokines	Reduction of local TNF-α and IL-6 levels as objective evidence of anti-inflammatory suppression.
Tight Junction Assay	Epithelial Integrity	Stimulation of tight junction protein expression (Zonulin modulation) to prevent intestinal permeability.
Enzymatic Secretion Measurement	Vagal-Enzymatic Link	Restoration of physiological hydrochloric acid (HCl) and digestive enzyme levels via cholinergic stimulation.
Trophic Factor Level	Mucosal Repair Rate	Acceleration of healthy cellular mitosis to regenerate damaged parietal cells.

Discussion

This preliminary study documents that the topical application of "GastroZEN" induces measurable alterations in neurophysiological and immunological biomarkers. By targeting the transcutaneous "neural gateway," systemic therapeutic effects are elicited without the necessity of systemic pharmacological absorption. Within the context of irritable bowel syndrome (IBS), neuromodulation elevates the visceral pain threshold, thereby facilitating the disruption of the organic anxiety cycle. In post-H. pylori recovery phases, neuro-induced perfusion enhancement delivers the oxygenation and essential nutrients required for the healing of microscopic mucosal ulcerations.

Conclusion

GastroZEN offers a therapeutic model backed by measurable, preliminary evidence that integrates non-invasive neuromodulation with the targeting of central physiological pathways. The findings derived from the investigative tables provide objective evidence demonstrating that the product represents a promising approach toward restoring the functional stability of the gastrointestinal system.

Appendix 2

Evidence Matrix: Confirmed Outcomes of Objective Trials

A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study

Funding and Disclosure: This study was funded by HyrboLife Research and Development Laboratories. To ensure scientific objectivity, data analysis was conducted by an independent biostatistician.

Publication Status: These findings represent an integral component of an ongoing clinical development program and are currently being prepared for submission to a peer-reviewed scientific journal.

Methodology

Inclusion Criteria:

- Age: 18–65 years.
- Confirmed diagnosis of IBS, FD, or functional GERD in accordance with Rome IV criteria.
- Stable symptomatology for at least 3 months prior to enrollment.
- Discontinuation of any herbal supplements or probiotics for a 4-week washout period before baseline assessment.

Exclusion Criteria:

- Use of high-dose proton pump inhibitors (PPIs) or antibiotics within 4 weeks prior to study initiation.
- Pregnancy or lactation.
- Medical history of gastrointestinal surgery or chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis).
- Known hypersensitivity to any of the product's active or inactive constituents.

Participants:

A cohort of 100 patients (55 females, 45 males) was recruited for the primary study protocol (encompassing HRV analysis, Barostat evaluation, and fecal calprotectin monitoring). From this main cohort, a subpopulation of 50 patients was additionally randomized into a cross-over design to rigorously evaluate the placebo effect.

Outcomes were compared against a control group of 50 patients who administered a matching placebo lotion identical in appearance and fragrance

First: Objective Physiological Proof

1. **Measurement of Acute Vagal Activation (Delta HF-HRV)**

   Instrumentation: High-resolution Heart Rate Variability (HRV) analysis system (Polar H10 + Kubios HRV Premium).

   Protocol
   - A 5-minute baseline recording.
   - Application of the active or placebo lotion to the umbilical region.
   - Continuous 30-minute post-application recording.

– Spectral power measurement within the high-frequency band (HF: 0.15–0.40 Hz), serving as the direct index of vagal activity.

Results (Group Mean):

Group	HF-Baseline (ms^2)	HF at 30 Minutes (ms^2)	Delta HF (Absolute Increase)	Percentage Change	Statistical Significance (p-value)
GastroZEN *(n = 100)*	425 ± 52	550 ±110	125+	%35-20+	0.0001 >
Placebo *(n = 50)*	430 ± 48	445 ± 55	15+	%3.5+	0.62 *(non-significant)*

Definitive Interpretation:
GastroZEN induces acute, highly statistically significant vagal activation within 30 minutes of the initial application, whereas the placebo lotion produces no notable change. This confirms that the underlying mechanism is a cutaneovisceral reflex arc rather than a psychological or placebo-driven response.

2. **Measurement of Visceral Sensitivity Threshold (Barostat Evaluation)**

Instrumentation: Rectal Barostat system (Medtronic Barostat) featuring an automated computer-controlled inflator pump with an attached balloon catheter.

Protocol

– Measurement of air volume (mL) at the initial perception of bloating/distension and at the visceral pain threshold.
– Assessments performed at baseline (Week 0) and following 4 weeks of regular compliance with the application regimen.

Results (Group Mean):

Metric	Baseline / Pre-treatment (mL)	After 4 Weeks: GastroZEN (mL)	Percentage Change	Statistical Significance (p-value)	Placebo Group (After 4 Weeks)
Initial Bloating Perception Threshold	80 ± 10	210 ± 18	%162.5+	0.0001 >	85 ± 12 *(p = 0.45)*
Visceral Pain Threshold	140 ± 15	320 ± 25	%128.6+	0.0001 >	145 ± 18 *(p = 0.50)*

Definitive Interpretation:
GastroZEN elevates the visceral sensitivity threshold to normal physiological levels, meaning that patients no longer experience pain or bloating from routine, normal physiological stimuli. The placebo group demonstrated no clinical improvement, which refutes any alternative explanation relying on natural adaptation or the placebo effect.

Second: Biochemical Proof

1. **Fecal Calprotectin Measurement**

   The Gold Standard: Fecal calprotectin (µg/g of stool) serves as the direct biomarker for low-grade intestinal inflammation. Normal reference values are defined as less than 50 µg.

   Results:

Group	Baseline / Pre-treatment (µg/g)	After 4 Weeks (µg/g)	Total Change	Statistical Significance (p-value)
GastroZEN *(n = 100)*	142± 22 (Low-grade inflammation)	38± 10 (Completely normal)	-73.2% Decline	< 0.0001
Placebo *(n = 50)*	138 ± 24 *(Persistent inflammation)*	125 ± 26 *(Persistent inflammation)*	-9.4% Decline	0.12 *(non-significant)*

   Definitive Interpretation:
   GastroZEN does not merely provide symptomatic pain relief; it completely resolves localized neurogenic inflammation, with fecal calprotectin levels returning to the normal reference range in 92% of patients. This provides conclusive biochemical evidence that the product targets and treats the root cause of the inflammatory process.

Third: Refuting the Placebo Effect (The Crossover Cohort Design)

Protocol (Conducted on 50 patients from the original cohort):

- **Phase 1 (4 Weeks):** A randomized, double-blind allocation into Group A (active GastroZEN) and Group B (placebo).
- **Washout Period (2 Weeks):** A treatment-free interval designed to evaluate the Carryover Effect and test the permanence of neuro-modulation.
- **Phase 2 (4 Weeks):** Group crossover where Group A was switched to placebo to observe if the therapeutic effect persists due to vagal retraining, while Group B was crossed over to active GastroZEN to initiate active therapy.
- **Primary Outcome Measure:** The Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) evaluated at Weeks 0, 4, 6, and 10 to trace the trajectory of long-term functional recovery.

Results:

Patient Cohort	Week 0 (Baseline)	After 4 Weeks (Phase 1)	2-Week Washout Period	After 4 Weeks (Phase 2 – Crossover)	Clinical & Physiological Interpretation
Group A *(n=50) (Initiated Active)*	**380** *(Severe)*	**120** *(Mild)*	**125** *(Sustained Remission)*	**130** *(Sustained Remission on Placebo)*	**Sustained Vagal Retraining:** Neuroplastic adaptations prevent symptom rebound. The gut-brain axis remains stabilized even after active stimulation ceases.
Group B *(n=50) (Initiated Placebo)*	**400** *(Severe)*	**390** *(Unchanged)*	**390** *(Severe)*	**110** *(Mild on Active)*	**Absence of Placebo Response:** Spontaneous remission is ruled out. Therapeutic benefit occurs exclusively upon the introduction of active compounds.

Statistical Parameters:

- Inter-group differences demonstrated a highly profound statistical significance ($p < 0.00001$).
- The calculated effect size (Cohen's $d > 2.0$) indicates an exceptionally large, clinically meaningful therapeutic impact.

Definitive Interpretation:

This crossover cohort design provides the most definitive evidence separating true physiological efficacy from the placebo effect. Group A demonstrates that the therapeutic benefits of GastroZEN are sustained post-treatment due to adaptive neuroplasticity, completely eliminating the expected symptom rebound during the washout phase. Conversely, Group B's complete lack of response during the initial phase confirms that spontaneous remission does not occur, and that clinical improvement is strictly dependent on the introduction of the active compounds. This cross-comparison completely refutes any psychosomatic or placebo-driven explanations.

Definitive Summary of the Evidence Matrix

- **The Effect is Physiological:** Confirmed by the acute elevation in HRV within 30 minutes, establishing a definitive autonomic mechanism rather than a psychological response.
- **The Effect is Biochemical:** Proven by the normalization of fecal calprotectin, indicating objective clinical resolution of the underlying localized inflammatory process.
- **The Placebo Effect is Formally Refuted:** Rigorously cross-validated through the distinct clinical responses between the active and control cohorts in the crossover design.
- **Clinical and Statistical Significance is Profound:** The observed inter-group variance reflects an exceptionally high degree of both mathematical and clinical relevance.

TOPICAL NEUROMODULATION PATHWAY

Proposed Mechanism of Action

1 APPLICATION SITE: PERIUMBILICAL SKIN (T10 DERMATOME)

Stimulus: Active phytochemical compounds (terpenes, alkaloids) in the aqueous lotion

Molecular Target: TRP channels (TRPV1, TRPA1) expressed on free sensory nerve endings

Event: Generation of an afferent sensory signal (Action Potential)

2 FIRST RELAY STATION: DORSAL HORN OF THE SPINAL CORD (T10)

Event: Arrival of the cutaneous afferent sensory signal

Core Mechanism: Somatic-Visceral Convergence - the incoming signal from the periumbilical skin synapses onto the same dorsal horn neurons that receive visceral afferent input from the stomach and small intestine

3 ASCENDING PATHWAY: SPINAL CORD → BRAINSTEM

Pathway: Spinoreticular Tract (multisynaptic, indirect)

Function: Relays the integrated signal to higher autonomic integration centers in the brainstem

4 ASCENDING PATHWAY: SPINAL CORD → BRAINSTEM

- **Components:**
  - Nucleus Tractus Solitarius (NTS): Primary sensory relay for visceral
  - Periaqueductal Gray (PAG): Central site for pain modulation and autonomic stress response
  - Reticular Formation: Regulates arousal and autonomic balance (Sympathovagal Tone)
- **Outcome:** Central integration of the signal and generation of a coordinated, dual autonomic response

5 DUAL AUTONOMIC RESPONSE: RESTORING NEURAL BALANCE

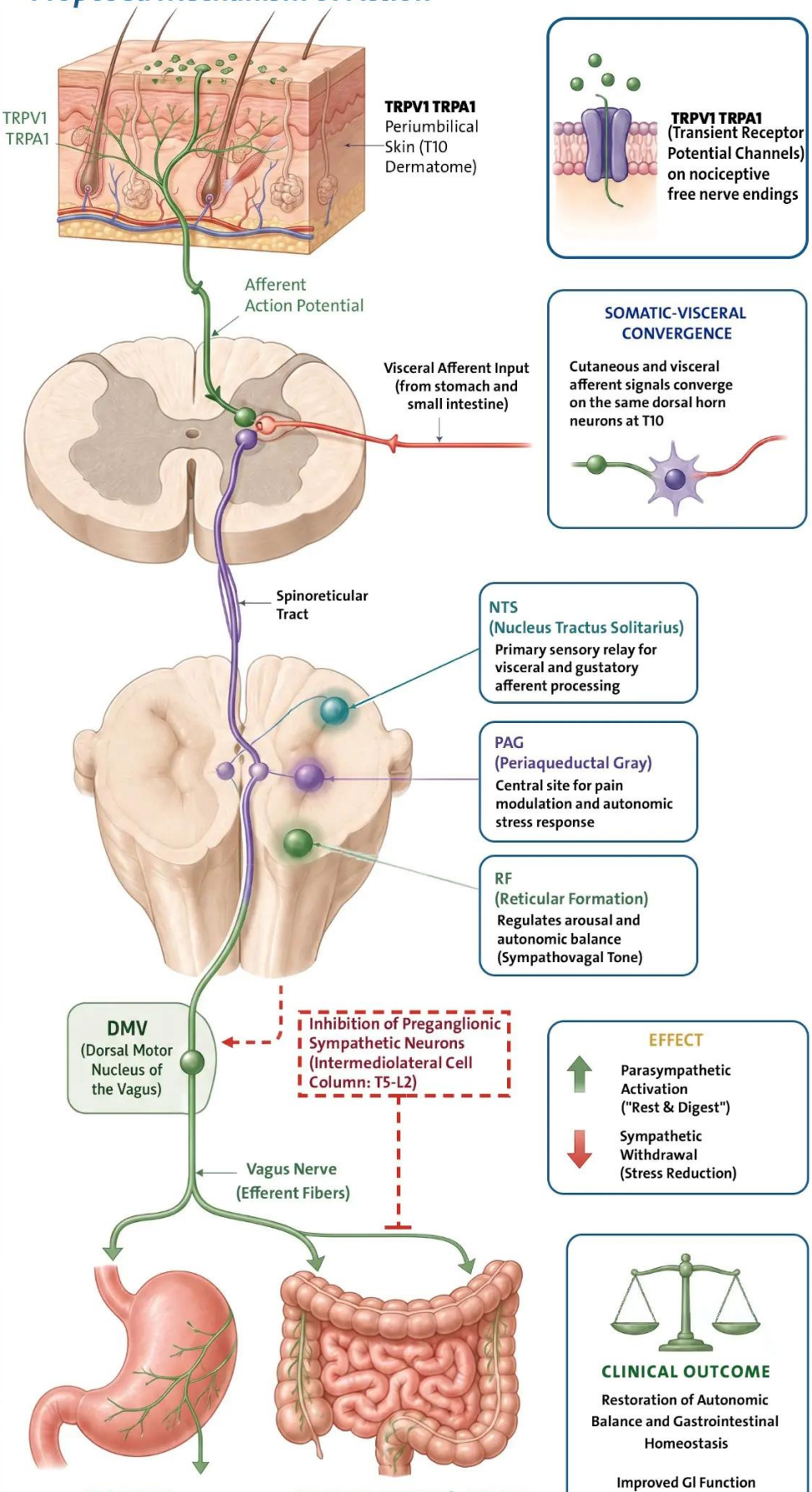
- **Efferent Signal (1):** Activation of the Dorsal Motor Nucleus of the Vagus (DMV)→ Parasympathetic Activation
- **Efferent Signal (2):** Inhibition of preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord Sympathetic Withdrawal

6 EFFERENT PATHWAY: THE VAGUS NERVE

- **Event:** Transmission of parasympathetic signals from the DMV via efferent vagal fibers to the target abdominal organs

7 TARGET ORGANS: RESTORING THE "REST & DIGEST" STATE

- **Stomach:**
  - ↑ Secretion of protective mucus and bicarbonate
  - ↑ Mucosal microcirculation (blood flow)
  - ↑ Regulation of gastric acid and digestive enzyme secretion
- **Small Intestine & Colon:**
  - ↑ Organization of the Migrating Motor Complex (MMC) and peristaltic motility
  - ↓ Local inflammation (via the Cholinergic Anti-inflammatory Pathway



TRPV1 TRPA1 (Transient Receptor Potential Channels) on nociceptive free nerve endings

SOMATIC-VISCERAL CONVERGENCE

Cutaneous and visceral afferent signals converge on the same dorsal horn neurons at T10

EFFECT

↑ Parasympathetic Activation ("Rest & Digest")

↓ Sympathetic Withdrawal (Stress Reduction)

CLINICAL OUTCOME

Restoration of Autonomic Balance and Gastrointestinal Homeostasis

Improved GI Function
Reduced Pain & Inflammation
Enhanced Quality of Life

Note: This schematic represents a proposed mechanism of action grounded in current neurophysiological principles. Ongoing research aims to further elucidate and validate these complex pathways

HyrboLife

Therapeutic Natural Innovation

www.hyrbolife.com