Evaluation of the effects of the dietary supplement EnzyFormula in functional disorders of the digestive system

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ABSTRACT

Digestion is a multifactorial process involving several organs and systems that exert mechanical (stomach and intestine), biochemical (liver and pancreas) and nervous control (central nervous system - CNS) under the homeostatic control system of the psycho-neuro-endocrine-immune (PNEI) axis.

About 20% of all Italians suffer from gastrointestinal diseases caused by unbalanced diet, unhealthy lifestyle, chronic use of medication and aging. In these situations, dysfunctions occur in the secretion of the digestive enzymes responsible for breaking down food and absorbing nutrients, with negative repercussions on liver and pancreas function.

The EnzyOBSERV observational clinical study focused on enzyme dysfunction associated with dyspepsia and malabsorption syndromes. The study was conducted on 100 subjects aged over 18 years enrolled in accordance with certain inclusion/exclusion criteria and treated with orally administered dietary supplement EnzyFormula at a dose of 2 tablets/day for a period of three months and followed up with evaluation of symptomatic parameters and safety monitoring of adverse events.

The data collected shows that dietary supplementation with EnzyFormula ensures a correct intake of enzymes and plant extracts that control digestive function with a reduction in symptoms associated with dyspepsia caused by reduced enzyme secretion and insufficient digestion of complex foods.

Introduction

Digestive enzymatic processes and their dysfunctions

Digestion is a complex, multifactorial process performed by a combination of functions involving a number of organs and systems, each one with different control roles: the stomach and small intestine perform mechanical control (in the stomach and intestine) and the liver and pancreas act as biochemical controllers for digestive processes; at the same time, the central nervous system (CNS), as part of the PNEI (Psycho–Neuro-Endocrine-Immune) system (1), contributes by processing and modulating the nervous and biochemical signals underlying the control mechanisms via digestive process feedback. A non-negligible role is played by the gut flora, which has a key role in digestive function, contributing to the processing of otherwise indigestible substances (thanks to its specific pool of enzymes) and to the maintenance of inflammatory intestinal homeostasis (2). The correct timing of the events associated with the intake of food and its digestion is dictated by the circadian rhythms and synchronised by cross-talk between the CNS and metabolic tissues (intestine, liver and pancreas) (3).

Enzyme function plays a crucial role in digestive processes and a large number of enzymes are involved: **salivary and pancreatic amylase, gastric pepsin, hepatic and pancreatic lipase, trypsin and chymotrypsin and intestinal lactase and peptidase** (4-7). The gastrointestinal tract responds to the ingestion of food with a complex and carefully controlled process (digestive timing) in order to make digestion and the absorption of nutrients as effective as possible: the presence of food in the stomach and, above all, duodenum, is the signal for the activation of the intestinal phase of the pancreatic secretion of amylase, trypsin, chymotrypsin and lipase and for the secretion of bile in the liver. It is interesting to observe how pancreatic and biliary secretion is regulated by precise, mutual neuro-immuno-endocrine mechanisms: it is stimulated by a number of gastrointestinal hormones such as gastrin, secretin, ghrelin and cholecystokinin (CCK) and is controlled by the central nervous system (CNS) through the vagus nerve (secretion stimulation) and the efferent fibres of the sympathetic nervous system (secretion inhibition) (8).

However, sympathetic pathway integrity is not essential for coordinated intestine function: indeed, there is an autonomic nervous system (enteric nervous system – ENS) that is sensitive to the same chemical stimuli perceived by the CNS. Its function is not merely digestive, but also immune and nervous, as in turn it secretes psychoactive substances (acetylcholine, dopamine and serotonin), which influence the activity of the central nervous system. These systems are known collectively as the gut-brain axis and represent a fundamental network for gastrointestinal tract functions (9; 10). The positive and negative feedback mechanisms that control the relationship between the consumption of food and the secretion of digestive enzymes in the gut-brain axis are central to the maintenance of digestive homeostasis: for example, an inadequate production of pancreatic enzymes leads to a reduction in CCK activity in the postprandial period (Figure 1) (11). The increase in circulating CCK, secondary to the attempt to overcome its reduced action, causes an alteration in the CNS response to eating; some of the most common symptoms of this imbalance are early satiety and increased postprandial drowsiness and heaviness. At this level a fundamental role is played by ghrelin and leptin, hormones that are produced in the stomach and adipose tissue respectively; the former stimulates the appetite and the latter regulates the feeling of satiety. The ghrelin/leptin balance is altered, for example, in the presence of liver dysfunctions: both hormones are up-regulated with a loss of homeostasis and increase in plasma glucose levels; these imbalances are also observed in the presence of malabsorption syndromes, where the reduction in the absorption of nutrients triggers a compensation mechanism based on an increase in ghrelin and, therefore, also in appetite and in obesity where leptin-resistance translates into an increase in adipose tissue (12-14).

In short, the close regulation of digestive mechanisms is essential for their correct operation and the onset of imbalances, specifically enzyme imbalances, substantially alters not merely the absorption of nutrients, but also the delicate neuropeptide cross-talk mechanisms between the ENS and CNS with repercussions on the individual's general psychophysical welfare (11; 15).

Epidemiology and most common symptoms

Recent data shows that 1 in 5 Italians either has "poor digestion" or suffers from fully blown gastrointestinal diseases (source: Italian Society of Gastroenterology, 2011). Digestion is strongly influenced by dietary excesses or stress: diets rich in fats and carbohydrates or frequent consumption of junk food are predisposing factors for the onset of digestive problems. Age (over the age of 40 digestive enzyme function can drop by as much as 50%), unhealthy lifestyles and chronic use of medicines also cause alterations in digestion (16 - 18).
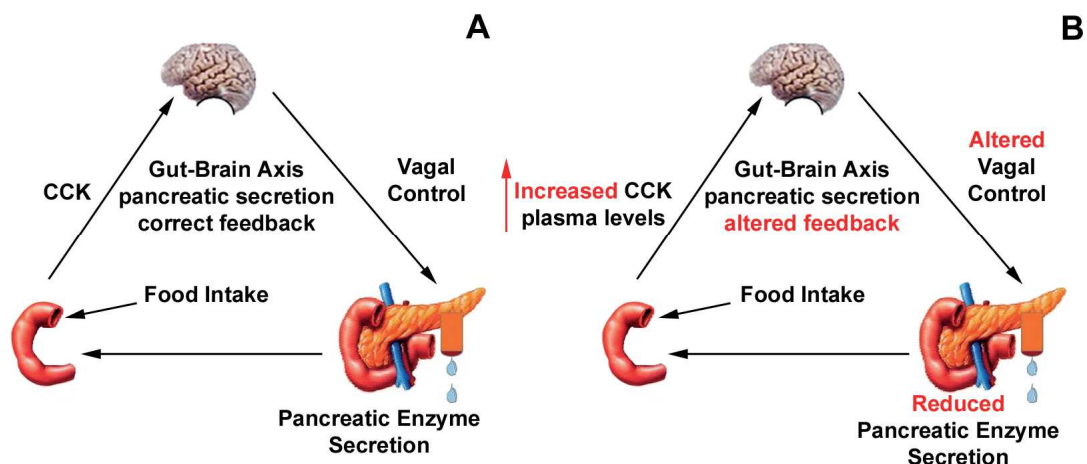
Figure 1: schematic representation of pancreatic secretion feedback mechanisms: A) physiological homeostatic situation; B) feedback mechanisms altered by the reduction in pancreatic enzyme secretion.

In these situations, there may be dysfunctions in the secretion of the digestive enzymes in charge of breaking down food and absorbing nutrients, with negative effects also on hepatic and pancreatic function; this leads to phenomena of reduced and/or incomplete digestion of complex foods such as milk and other dairy products, sugars, proteins and lipids (19; 20). The symptoms connected to these dysfunctions are **postprandial heaviness and drowsiness, an increase in fermentation phenomena and intestinal putrefaction, abdominal bloating, intestinal gas** and **headache.** The persistence of enzyme production alterations leads to a reduced absorption of nutrients, liver function alterations and changes in the composition of gut flora.

The EnzyOBSERV clinical study
The EnzyOBSERV observational clinical study focused on enzyme dysfunctions, common causes of dyspeptic phenomena and malabsorption syndromes.
The aim of the EnzyOBSERV study is to evaluate the activity of the dietary supplement **EnzyFormula (Guna S.p.a. – Italy)** in the treatment of gastrointestinal diseases caused by enzyme activity dysfunctions. The dietary supplement EnzyFormula is attributed enzyme support activity, by virtue of its particular and balanced formulation containing: amylase, lactase, lipase and cellulase; bromelin and papain (21); dry extract of *Phyllantus niruri* (contributes to improving liver function) (22; 23), *Fumaria officinalis* (helps rebalance liver-biliary-pancreatic function and is a natural anti-spastic) (24) and *Curcuma longa* (antioxidant and hepatoprotector) (25-27); niacin (Vitamin PP, a useful cofactor for the maintenance of gastric and intestinal mucosal homeostasis) (28) and superoxide dismutase (SOD, an antioxidant) (29).

Materials and methods
The product used in the EnzyOBSERV study is **EnzyFormula**, a dietary supplement in the form of differentiated-release gastroresistant tablets containing (per tablet): *Phyllantus niruri* L. dry extract (leaves and flowers) 200 mg; enzyme blend (amylase, lactase, lipase and cellulase) 100 mg; *Fumaria officinalis* L., plant, dry extract 100 mg; Bromelin 50 mg; Papain 50 mg; *Curcuma longa* L., root, dry extract 40 mg; Vitamin PP (Niacin) 36 mg; Superoxide Dismutase (SOD) from melon juice (*Cucumis melo* L., fruit) 5 mg. Anti-caking agents: cross-linked sodium carboxymethyl cellulose, silicon dioxide, magnesium stearate, talc, coating agents: hydroxypropyl cellulose, carnauba wax; loading agents: microcrystalline cellulose, calcium phosphate, maltodextrin; sweetener: sucralose. The enzyme blend, combined with *Phyllantus niruri* L., *Fumaria officinalis* L. and Vitamin PP, is contained in the rapid-release outer layer. *Curcuma longa* L. and superoxide dismutase on the other hand are contained in the inner, slow-release gastro-resistant layer.
The substances contained in the two layers and their biological activity are summarised in Table 1.

"FAST" OUTER LAYER	
ENZYMES (obtained using biotechnology by fermentation on maltodextrin)	**FUNCTION**
Lactase or β-galactosidase	Hydrolysis of lactose's β-D-galactoside bond
Amylase	Hydrolysis of the polysaccharides' α-1,4-glycosidic bonds
Lipase	Triglyceride hydrolysis
Cellulase	Cellulose hydrolysis
Papain and bromelin	Protein hydrolysis
PLANT INGREDIENTS	**FUNCTION**
Phyllantus niruri L. dry extract of flowers and leaves	Maintains physiological hepatocyte function
Fumaria officinalis L. dry plant extract	Purifying-diuretic, bile-stimulating and bile-regulating function
VITAMINS	**FUNCTION**
Vitamin PP	Maintains mucosal condition and function Lowers triglyceride and LDL cholesterol values Protects micro-vessels against oxidative damage Nutrient absorption and metabolism
"SLOW" INNER LAYER	
PLANT INGREDIENTS	**FUNCTION**
Curcuma longa L. (dry root extract, cont. 98%)	Antioxidant, anti-inflammatory and antiviral properties
ANTIOXIDANTS	**FUNCTION**
Superoxide dismutase (SOD) melon juice extract (*Cucumis melo L.* fruit) concentrate (Extramel®)	Reduces oxidative stress phenomena

Table 1: ingredients and fundamental characteristics of the "FAST" and "SLOW" controlled release layers of EnzyFormula.

Study design

The EnzyOBSERV clinical study is a multicentre (11 centres throughout Italy) observational study aimed at evaluating the activity of EnzyFormula in the treatment of functional disorders of the gastrointestinal tract.

Over a two-month period (February – April 2013) 100 subjects were enrolled. An initial screening visit (T0) was performed to recruit patients meeting the protocol's inclusion and exclusion criteria (Table 2). Only subjects who signed the informed consent form were included in the study. All enrolled subjects underwent a second visit after three months of treatment (T3 months) for endpoint assessment.

All patients were treated with EnzyFormula, administered by mouth at a dose of 2 tablets/day (one tablet before each main meals) for three consecutive months.

Each investigator followed the subjects enrolled in the trial throughout the treatment period in order to evaluate safety through the monitoring of any adverse events (AEs).

The study lasted a total of 5 months (2 months' enrolment plus 3 months of treatment) and took place between February and July 2013. Participating subjects recorded in their patient diaries (Table 3) the frequency and severity of the following symptoms: **borborygmus, headache, intestinal gas, postprandial heaviness and postprandial drowsiness.** The parameter analysis data was obtained from the diaries at T0 and subsequently once a month (T1; T2; T3) until the end of treatment.

Inclusion criteria	Exclusion criteria
Eligible subjects are male and females meeting the following criteria: Adult outpatients with digestive disorders and the following characteristics: - Age between 40 and 60 years; - Subjects with functional GI tract disorders not being treated with other products containing digestive enzymes; - Patients able to comply with study procedures; - Patients able to understand and sign the informed consent form and consent to the handling of their	Male and female subjects are **not eligible** for study participation if they: - Have coeliac disease; - Have liver or pancreatic failure; - Have gastric or duodenal ulcers; - Have had a cholecystectomy; - Have inflammatory bowel disease, Crohn's disease, etc.; - Are taking buffer products; - Are on treatment with proton pump inhibitors (PPI);

personal data.	• Are being treated with H2-blockers;
	• Are on chemotherapy;
	• Are pregnant or breastfeeding.
	• Are potentially allergic to the ingredients of EnzyFormula.

Table 2: inclusion and exclusion criteria for the EnzyOBSERV multicentre clinical study

Results

Enrolled subjects indicated on the patient diary the frequency and severity of the symptoms evaluated subjectively using a scale marked with the symbols (+), (++), (+++), (++++) (Table 3).

The data collected during the period of treatment with EnzyFormula was processed by allocating each parameter a numerical score obtained by converting the diary symptom scale and indicating the frequency with which the specific episode occurred. The data was subsequently statistically analysed to assess its significance.

Borborygmus

Following treatment with EnzyFormula the episodes of borborygmus reported by patients dropped significantly compared to the baseline: T0 = 2.51 SD ± 0.88; T3 = 1.24 SD ± 0.56; ΔT0-T3= **-50.6%**; Friedman test: $p < 0.00001$ (Figure 2A). Each measurement is statistically significant compared to the previous one: this suggests that EnzyFormula's action is rapidly established and is enhanced and maintained with regular use of the product.

Headache

Headaches with a rapid post-prandial onset were significantly lower than baseline at the end of treatment with EnzyFormula: score recorded at baseline T0 = 1.64 SD ± 0.93; score at T3 = 1.20 SD ± 0.58; ΔT0-T3= **-26.83%;** Friedman test: $p < 0.00001$ (Figure 2B).

Multicentre clinical study to evaluate the efficacy of EnzyFormula for the treatment of functional gastrointestinal disorders

PATIENT DIARY

PATIENT'S INITIALS:	
DATE OF BIRTH:	
TELEPHONE NUMBER:	

Diagnosis:

SYMPTOM TREND
(+)=NO symptoms
(++)= MILD symptoms
(+++)= MODERATE symptoms
(++++)= SEVERE symptoms
* for "postprandial satiety": *(+)= NO satiety, (++)= PARTIAL satiety, (+ + +)= TOTAL satiety*

SYMPTOMS	T0 Before treatment	T1 1 month	T2 2 months	T3 3 months
FEELING OF POSTPRANDIAL HEAVINESS				
FEELING OF POSTPRANDIAL DROWSINESS				
HEADACHE				
ABDOMINAL GAS (abdominal bloating due to gas or air in the intestine)				
BORBORYGMUS (tummy rumbling)				
POST-PRANDIAL SATIETY*				

1) Patient's acceptance and appreciation of the product: *(tick appropriate box)*	POOR	
	SATISFACTORY	
	EXCELLENT	
2) Adverse reactions:	YES	NO

If so, which:

I hereby authorise the handling of my personal data pursuant to Legislative Decree 196 of 2003

Patient's signature:

Table 3: page of the patient diary for the EnzyOBSERV multicentre clinical study

Intestinal gas

Intestinal gas reduced significantly with use of EnzyFormula from the baseline to the end of treatment (ΔT0-T3= **-55.50%**; Friedman test: p<0.00001 (T0 = 3.20 SD ± 0.82; T3 = 1.42 SD ± 0.70) (Figure 2C). Each measurement is statistically significant compared to the previous one: this suggests that EnzyFormula's action is rapidly established and is enhanced and maintained with regular use of the product.

Postprandial heaviness

The score associated with postprandial heaviness improves at the end of treatment from T0 = 2.78 SD ± 0.84 to T3 = 1.306 SD ± 0.60 (Friedman test: p<0.00001) with a ΔT0-T3 = **-52.88%** (Figure 2D). Each measurement is statistically significant compared to the previous one: this suggests that EnzyFormula's action is rapidly established and is enhanced and maintained with regular use of the product.

Postprandial drowsiness

Postprandial drowsiness decreases significantly during treatment with EnzyFormula: between baseline and the end of treatment there is a ΔT0-T3 = **-48.53%** with a mean score at T0 = 2.39 SD ± 0.97 and at T3 = 1.23 SD ± 0.5; (Friedman test: p<0.00001) (Figure 2E). Each measurement is statistically significant compared to the previous one: this suggests that EnzyFormula's action is rapidly established and is enhanced and maintained with regular use of the product.

Adverse event reporting and the safety of treatment

For the entire duration of the treatment the investigators did not record any adverse events reported by enrolled subjects, allowing us to confirm the product's safety and use according to the protocol.

Product compliance

Patient compliance for treatment with EnzyFormula was seen to be very good, in terms of the item "patient's acceptance and appreciation of the product", which was "excellent" in most patient diaries.

Discussion

The EnzyOBSERV observational clinical study was conducted to evaluate the efficacy of the dietary supplement EnzyFormula in the treatment of digestive function alterations. EnzyFormula is composed of a complex of digestive enzymes, vitamin PP and plant extracts able to rebalance the composition of the hepato-pancreatic enzyme pool and the function of the areas involved in digestive processes, which are altered by poor diet, old age and unwholesome lifestyles.

One fundamental characteristic of EnzyFormula is the differentiated component release mechanism, which guarantees excellent segmental (in different areas of the gastrointestinal tract) and temporal distribution of the active ingredients, in line with physiological digestive timing.

Enzymes and plant complexes are contained in the rapid-release outer layer; they are therefore released in the stomach and duodenum within 60 minutes of administration, making them rapidly and completely available to supplement the enzyme pool, when the food reaches the stomach. The acidic pH of the stomach environment means that the plant extracts and vitamin PP are rapidly mobilised, which maximises their hepatoprotective and purifying action and their adjuvant activity in the absorption of nutrients. The extract of *Curcuma longa* L. and superoxide dismutase contained in the slow-release gastro-resistant layer are released in the small intestine so that they can exert their antioxidant and hepatoprotective activity, acting as oxygen free radical scavengers.

The results obtained in the EnzyOBSERV study show that the use of EnzyFormula in the presence of digestive disorders is efficacious in significantly reducing the symptoms monitored. All the parameters recorded show a significant improvement, which highlights the efficacy of treatment with EnzyFormula; the reduction in the frequency with which the disorders present varies from a minimum of **-26.83%** (for headache) to a maximum of **-55.50%** (for intestinal gas) and the remaining symptoms have a mean value of around **-50%**. Statistical analysis shows how a significant reduction in dyspeptic phenomena associated with poor digestion occurs in the first month of treatment, between T0 and T1, thereby showing that treatment with EnzyFormula boasts the dual advantage of rapidity of action and a prolonged action over time.

This digestion regulation action not only has positive effects on the symptoms experienced by patients, it also reduces the conditions of stress the organs and segments of the gastrointestinal tract are subject to (reduction of digestive involvement). The liver and pancreas are affected in a negative way by enzyme imbalances caused by the alteration of the feedback mechanisms that control enzyme secretion; the presence of hepato- and pancreatoprotective substances such as the extracts of *Phyllantus niruri* and *Fumaria officinalis* helps the enzyme pool to restore hepato-bilio-pancreatic homeostasis. The intestinal wall also suffers the effects of digestive function alteration: the presence of partially or completely indigested food reduces the enterocytes' capacity to absorb nutrients and the presence of fermenting material can cause the onset of inflammatory states. Vitamin PP, an ingredient of EnzyFormula present in significant amounts (225% of the RDA) supports the physiological function of the intestine wall in combination with the dry extract of *Curcuma longa* L. and with superoxide dismutase (SOD), as the former acts as a cofactor for digestive

enzyme reactions and the other substances act as antioxidants able to rebalance any oxidative stress phenomena present in the intestinal wall.
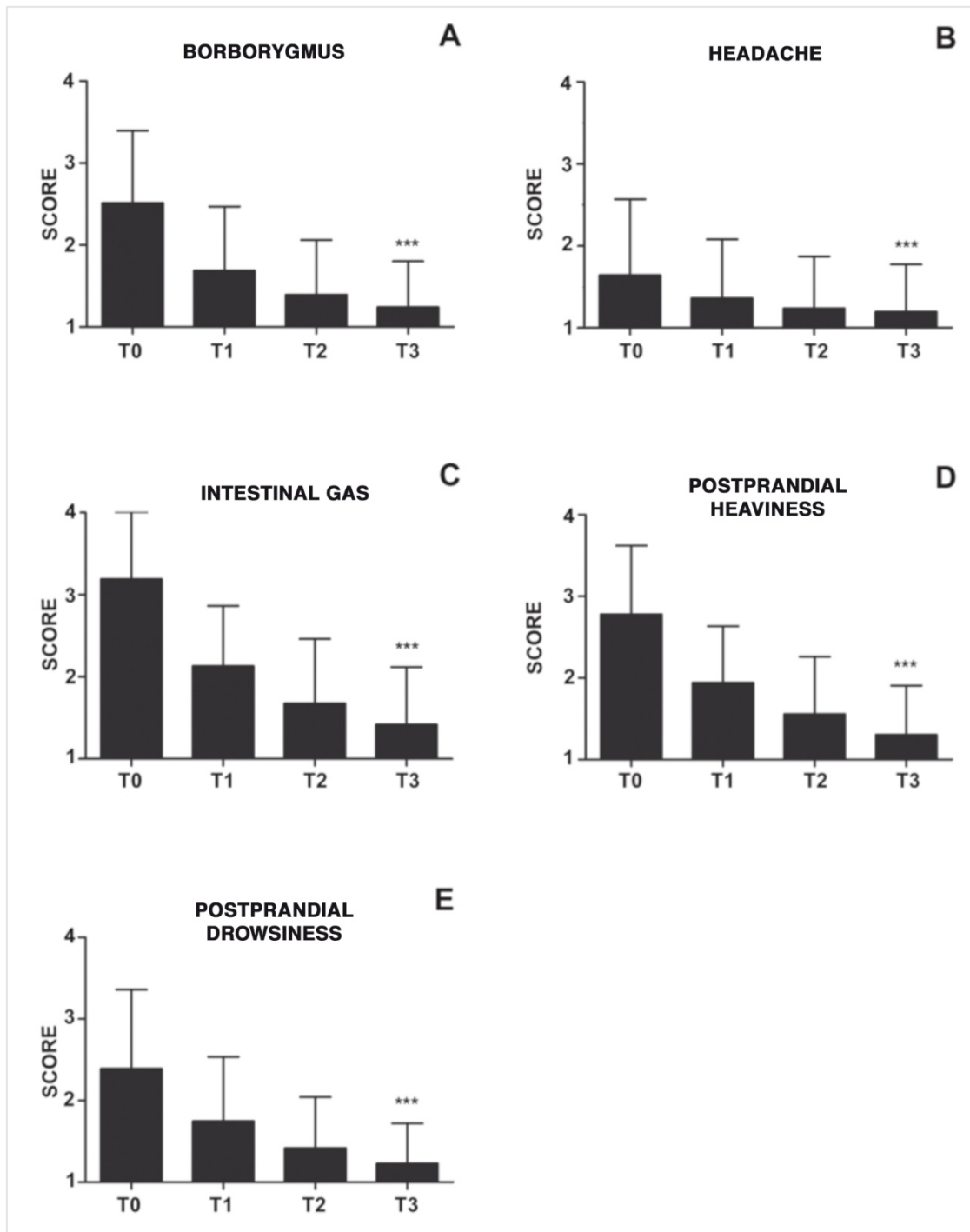
Figure 2: graph showing the efficacy of treatment of functional dyspepsia with EnzyFormula. EnzyFormula's action is established rapidly and is boosted and maintained with regular use of the product, thereby significantly improving the symptoms.

Conclusion

The data collected during the EnzyOBSERV observational study shows that the use of the dietary supplement EnzyFormula guarantees an optimum intake of enzymes and plant extracts that help control digestive function, with a significant reduction in the conditions of malaise associated with dyspepsia due to reduced enzyme secretion and inadequate digestion of certain foods such as milk and other dairy products, complex meat and cheese proteins, fibre-rich vegetables and particularly fatty foods.

The balanced intake of digestive enzymes and the antioxidant activity of some of EnzyFormula's plant ingredients allow a reduced digestive commitment, making the product a supplement with an anti-ageing action.

EnzyFormula boasts a number of special characteristics such as its complete formulation, the high availability and synergy of its active ingredients, rapidity of action, capacity to maintain the same action over time and observance of the physiological timing of digestion. These characteristics mean that EnzyFormula is not only indicated in the treatment of functional dyspepsia but also as an efficacious co-adjuvant in the treatment of dysbiosis, malabsorption syndromes and obesity or in cases in which hepato-pancreatic function requires support.

References

1. Ader R. Psychoneuroimmunology IV edition vol. 1 e 2. Amsterdam: Academic Press, 2007.
2. Collins SM, Bercik P. The Relationship Between Intestinal Microbiota and the Central Nervous System in Normal Gastrointestinal Function and Disease. Gastroenterology 2009; 136:2003–2014.
3. Stenvers DJ, Jonkers CF, Fliers E, Bisschop PH, Kalsbeek A. Nutrition and the circadian timing system Prog Brain Res. 2012;199:359-76
4. Maldonado-Valderrama J, Wilde P, Macierzanka A, Mackie A. The role of bile salts in digestion. Adv Colloid Interface Sci. 2011 Jun 9;165(1):36-46.
5. Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright (1993). *Human Biology and Health*. Englewood Cliffs, New Jersey, USA: Prentice Hall
6. Roxas M. The role of enzyme supplementation in digestive disorders. Altern Med Rev. 2008 Dec;13(4):307-14
7. Srirama R, Deepak HB, Senthilkumar U, Ravikanth G, Gurumurthy BR, Shivanna MB, Chandrasekaran CV, Agarwal A, Shaanker RU. Hepatoprotective activity of Indian Phyllanthus. Pharm Biol. 2012 Aug;50(8):948-53.
8. Jaworek J, Nawrot-Porabka K, Leja-Szpak A, Konturek SJ. Brain-gut axis in the modulation of pancreatic enzyme secretion. J Physiol Pharmacol. 2010 Oct;61(5):523-31.
9. Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease.Gastroenterology. 2013 Jan;144(1):36-49.
10. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. J Physiol Pharmacol. 2011 Dec;62(6):591-9.
11. Garces MC, Gomez-Cerezo J, Codoceo R, Grande C, Barbado J, Vazquez JJ. Postprandial cholecystokinin response in patients with chronic pancreatitis in treatment with oral substitutive pancreatic enzymes Dig Dis Sci. 1998 Mar;43(3):562-6.
12. Kerem M, Bedirli A, Pasaoglu H, Unsal C, Yilmaz TU, Ofluoglu E, Sahin TT. Role of ghrelin and leptin in predicting the severity of acute pancreatitis. Dig Dis Sci. 2007 Apr;52(4):950-5.
13. Gonnissen HK, Hulshof T, Westerterp-Plantenga MS. Chronobiology, endocrinology, and energy- and food-reward homeostasis.Obes Rev. 2013 May;14(5):405-16.
14. Peracchi M, Conte D, Terrani C, Pizzinelli S, Gebbia C, CappielloV, Spada A, Bardella MT. Circulating ghrelin levels in celiac patients. Am J Gastroenterol. 2003 Nov;98(11):2474-8.
15. Konturek PC, Konturek SJ, Ochmański W. Neuroendocrinology of gastric H+ and duodenal HCO3- secretion: the role of braingut axis. Eur J Pharmacol. 2004 Sep 19;499(1-2):15-27.
16. Vellas B, Balas D, Moreau J, Bouisson M, Senegas-Balas F, Guidet M, Ribet A. Exocrine pancreatic secretion in the elderly. Int J Pancreatol. 1988 Dec;3(6):497-502.
17. Bernardis LL, Lee PC, Brooks S, Lebenthal E. Normal pancreatic and intestinal enzymes in hypophagic growth-retarded rats that received dorsomedial hypothalamic lesions shortly after weaning. Pharmacol Biochem Behav. 1984 Aug;21(2):245-53.
18. Gillett RC Jr, Norrell A. Considerations for safe use of statins: liver enzyme abnormalities and muscle toxicity. Am Fam Physician. 2011 Mar 15;83(6):711-6.
19. Tomasik P, Horton D. Enzymatic conversions of starch. Adv Carbohydr Chem Biochem. 2012;68:59-436.
20. Layer P, Groger G. Fate of pancreatic enzymes in the human intestinal lumen in health and pancreatic insufficiency. Digestion.1993;54 Suppl 2:10-4.
21. Hiraganahalli BD, Chinampudur VC, Dethe S, Mundkinajeddu D, Pandre MK, Balachandran J, Agarwal A. Hepatoprotective and antioxidant activity of standardized herbal extracts. Pharmacogn Mag. 2012 Apr;8(30):116-23.

22. Manjrekar AP, Jisha V, Bag PP, Adhikary B, Pai MM, Hegde A, Nandini M. Effect of Phyllanthus niruri Linn. treatment on liver, kidney and testes in CCl4 induced hepatotoxic rats. Indian J Exp Biol. 2008 Jul;46(7):514-20.
23. Boim MA, Heilberg IP, Schor N. Phyllanthus niruri as a promising alternative treatment for nephrolithiasis. Int Braz J Urol. 2010 Nov-Dec;36(6):657-64.
24. Campanini E. "dizionario di fitoterapia e piante medicinali" Tecniche Nuove 2004; 216-219
25. Sheldon S. H. "physician's desk reference" CEC Editore 2010.
26. Majeed M, et al. "Curcuminoids-antioxidant phytonutrients" 1995. 27. Majeed M, et al. "Turmeric and the healing curcuminoids" Sabinsa 1996.
28. MacKay D, Hathcock J, Guarneri E. Niacin: chemical forms, bioavailability, and health effects. Nutr Rev. 2012 Jun;70(6):357-66.
29. Yasui K, Baba A. Therapeutic potential of superoxide dismutase (SOD) for resolution of inflammation. Inflamm Res. 2006 Sep;55(9):359-63.