Desynchronisation of the HPA axis, stress and Chronic Fatigue Syndrome

Observational multicentre study on Tonicoguna and Vit Formula™ to support the function of the Hypothalamic - Pituitary - Adrenal axis

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Abstract

Stress is defined as a positive biological-behavioural reaction linked to the preservation of life through the processes of natural selection. Under normal conditions, reaction to a stressor event leads to a time-limited physiological activation of the hypothalamic-pituitary-adrenal (HPA) axis that is pivotal for adaptation of the organism to changes in environmental stimuli. In the presence of chronic stress, the HPA axis is hyper-activated and de-synchronized with the onset of Chronic Fatigue Syndromes and loss of psycho-neuroendocrine-immune homeostasis caused by the alteration of the PNEI axis.

The TONICOBSERV clinical observational study focused on Chronic Fatigue Syndromes with de-synchronization of the HPA axis associated with chronic stress, with the aim of evaluating the effectiveness of the experimental treatment of the syndrome with dietary supplements Tonicoguna and VIT Formula™.

The study was conducted on 70 subjects aged between 20 and 60 years enrolled in accordance with defined inclusion/exclusion criteria and treated with orally administered dietary supplements Tonicoguna and VIT Formula™ at a dose of one sachet/day for each of the two products for a period of four weeks and followed up with an evaluation of symptomatic parameters and safety through the monitoring of adverse events.

The data collected shows that dietary supplementation with Tonicoguna and VIT Formula™ ensures an optimum intake of vegetable substances, vitamins, minerals and other micronutrients that play an active role in reducing the fatigue syndromes caused by chronic stress.

Introduction

The stress activation/deactivation circuit

The term "stress", which was originally employed in engineering to indicate the tension and strain that a stiff material is subject to in loaded conditions, was first used in biology by **Hans Selye,** who gave it this unequivocal definition: "*Stress is an essential response for life, complete freedom from stress is death. Contrary to what one may think, we must not and cannot avoid stress, but we can tackle it in an effective way, thus drawing an advantage from it, learning more about its mechanisms and adapting our philosophy of life to it"* (1).

In 1936, Selye observed that laboratory animals inoculated with stressor substances, reacted by presenting with a common **syndrome**. This syndrome was characterised by **adrenocortical hypertrophy, thymus** and **lymph gland atrophy** and the onset of **gastric ulcers** and represented the non-specific response with which the body adapted to the changed physiological and psychological demands it was subject to (2). The most recent developments in the concept of stress have led the scientific community to define it as a broad biological and behavioural reaction aimed at preserving life and the consequence of a process of natural selection, which gives stress a decidedly positive meaning (3). This view is fully valid when the source of stress is not particularly violent and homeostatic control systems are effective.

As Selye observed, in such situations, it is in particular the hypothalamic – pituitary - adrenal (**HPA**) axis that is physiologically activated, a reaction that helps adapt the body to changes in the environmental stimuli with which the human being interacts constantly (4).

The adaptive response is composed of three elements: stressor, individual and environment.

1. **Stressor:** stressors can be physical (electric shock, exposure to the cold, etc.) (5), metabolic (glycaemia level alterations) (6), psychological (an exam or interview) (7; 8), or psychosocial (loss or bereavement) (9). Despite causing general response mechanism activation, each stressor is characterised by a preferential stimulation of one or more systems (nervous or endocrine). In addition to the nature of the stressor, its intensity, frequency, duration, degree of novelty, predictability and, above all, its evitability, are also important: an event that has never been experienced before, that is unpredictable or inevitable, generates a more intense response than a known or avoidable stimulus (10).

2. **Individual:** the stressor's field of action; in the individual response to the stressor, in addition to age and sex, decisive roles are played by the efficiency of the psycho-neuroendocrine-immune (PNEI) axis (11) and the personality profile (12). Old age is generally considered a phase of poor adaptive capacity and is associated with a higher response to stress. Diet, with its ability to influence the homeostasis of the entire body, plays a central role, as does lifestyle (13).

3. **Environment:** this is the third component (inside or outside the individual) of the response to stress and is the **source** of stressors. When we refer to an external environment we do not merely mean the geoclimatic characteristics of a place, but also the aspects associated with social interaction and the individual's occupation (14).

HPA axis dysregulation: chronic stress

One of the main causes of a weakening and imbalance of the neurovegetative functions is a **continuous involvement** of the hypothalamic – pituitary – adrenal (**HPA**) axis. The chronic activation of the HPA axis is known as "**Chronic Stress Syndrome**" and involves the progressive exhaustion of the body's ability to synthesise the neuro-hormonal mediators responsible for controlling the HPA axis (10; 15). This condition occurs with the loss of the ability to modulate the neuroendocrine axis (**HPA axis desynchronisation**) (Figure 1) with repercussions on the neurovegetative and emotional systems and on the immune system (16; 17); "chronic stress" is therefore a severe alteration of the PNEI system, with loss of psycho-neuroendocrine-immune homeostasis.

The entire PNEI axis and all 3 homeostatic regulation systems are affected by a condition of chronic stress and the effects of hypercortisolaemia:

1) the **endocrine system**, by the long system of negative retroaction with a down-regulation of hypothalamic and pituitary function;

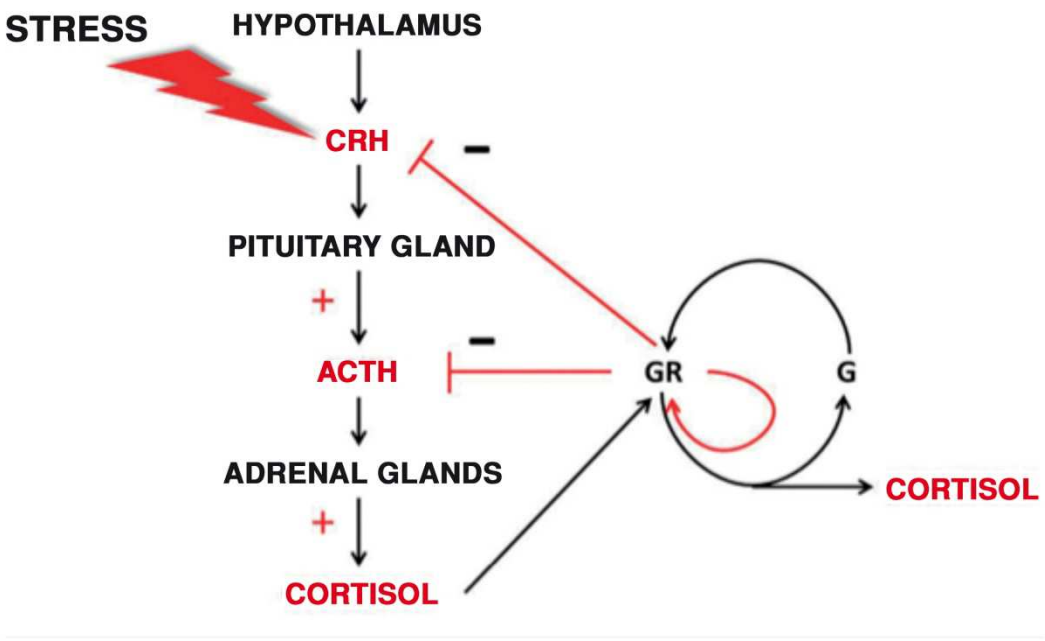

Figure 1: cortisol regulation system in the HPA axis. Chronic stress causes the hypothalamic secretion of the corticotropin-releasing hormone (CRH); it diffuses in the pituitary gland activating ACTH (adrenocorticotropic hormone); ACTH activates the production of cortisol in the adrenal glands. Cortisol binds to the glucocorticoid receptor (G) and the resulting complex (GR) dimerises. Cortisol down-regulates its own production through the GR complex that binds both CHR and ACTH to form a negative feedback circuit.

2) the **central nervous system**, due to the effects on the amygdala and the hippocampus;

3) the **immune system**, due to the direct down-regulation of Th1 and the indirect down regulation of $CD8^+$.

The concomitant presence of all the body's systemic reactions caused by a prolonged exposure to systemic stress is known as **general adaptation syndrome** (**GAS**) (18; 19) and it takes place through 3 sequential phases:

- **Alarm phase:** phase characterised by an acute stress reaction in which the body's defences are mobilised (pituitary-adrenal hyperactivation).

- **Resistance phase:** the phase in which the organism is engaged in dealing with the stress; the reaction to the stressor is still active and cortisol hyperproduction continues, however the equilibrium starts to change. The continuous production of cortisol leads to gradual immunodeficiency and, if the resistance phase is prolonged over time, the susceptibility to infection increases dramatically, and in the same way there can be a dramatic reduction in the immunosurveillance function exerted by the *T suppressors* in the differentiation and proliferation of tumour cells.

- **Exhaustion phase:** this phase occurs when the exposure to stress is prolonged for an abnormal length of time, the adrenal cortex goes into a state of functional exhaustion with a reduction in cortisol synthesis and the onset of pathological conditions that are difficult to reverse.

The chronicisation of stress is associated with the appearance of a cascade of typical symptoms (**distress** phase): chronic fatigue, interpersonal problems with self-isolation, severe emotive disorders such as serious irritability and aggressiveness, onset of chronic pain (muscular stiffness, bruxism, weekend headaches, etc.), onset of stress conditions caused by the loss of PNEI homeostasis (infections, ulcers, colitis, hypertension, asthma) (20-22). These conditions associated with HPA axis alteration are similar to those associated with chronic fatigue syndrome (**CFS**) (23-25). A concise summary of distress symptoms is given in Table 1.

Physical symptoms	***Mental symptoms***	***Behaviour disorders***
• tachycardia, tight feeling in the chest • dizziness, muscle pain, jaw tightening and nocturnal teeth grinding (bruxism) • irritable bowel, bloated feeling after meals, nausea, acidity and stomach pains • reduction in libido	• depression, anxiety • apathy, chronic fatigue • concentration problems, memory loss	• accelerated speech, often cutting of the end of sentences • excessive and neurotic hunger or loss of appetite • easy irritability • hyperactivity, insomnia and continuous drowsiness • fast, shallow breathing

Table 1: list of the most common symptoms associated with chronic stress phenomena.

Inclusion criteria	Exclusion criteria
Eligible subjects are male and female patients who meet the following criteria: • adult outpatients with HPA axis dysregulation; • aged 20 – 60 years; • subjects presenting with symptoms typical of chronic fatigue syndrome: chronic listlessness, psycho-physical exhaustion, sleep disorders, mnemonic-cognitive disorders; • persistence of the condition for at least 6 months; • patients able to comply with study procedures; • patients able to understand and sign the informed consent form and consent to the handling of their personal data.	**Non-eligible** subjects are male and female patients who: • regularly use sleep medication; • are on oestrogen-progestin treatments; • have primary hypertension; • have Addison's disease or Cushing's syndrome; • are on anticoagulants or antiallergic medication; • are positive for anti-EBV (Epstein-Barr virus) or anti-HHV6 (Human Herpes Virus type 6) antibodies; • have an active tumour; • are pregnant or breastfeeding; • have coeliac disease; • are potentially allergic to the ingredients of Tonicoguna and VIT Formula™

Table 2: inclusion and exclusion criteria used during the enrolment phase of the TONICOBSERV Multicentre observational clinical study.

Management of chronic stress and the TONICOBSERV study

By PNEI axis modulation, the human body constantly attempts to preserve or restore the conditions of general homeostasis. Exceeding the pathological stress threshold entails the loss of homeostasis and in such conditions it is often no longer enough to eliminate, when possible, the stressors or take action against unwholesome lifestyles: appropriate external support is required.

Psychological counselling, a healthy diet, correct physical activity and relaxation techniques are the most efficacious tools for intervention in situations of chronic stress.

The TONICOBSERV study was designed to evaluate the activity and efficacy of the combination of two dietary supplements, **Tonicoguna and VIT Formula™**, when taken by subjects with HPA axis alteration with consequent onset of CFS. The formulation of the two tested products was developed to provide a fundamental intake of vitamins and plant extracts that are effective in chronic HPA axis activation syndromes, such as **chronic fatigue, psycho-physical exhaustion, sleep disorders, headache, immune response alteration and mnemonic-cognitive deterioration**.

Study design

The TONICOBSERV clinical study is a multicentre (12 centres throughout Italy) observational study lasting 4 months (3 months' enrolment and 4 weeks of treatment) between March and June 2013.

The purpose of the TONICOBSERV study was to evaluate the clinical improvement of a group of patients with symptoms associated with HPA-axis dysregulation treated with **Tonicoguna** (GUNA S.p.A. Milan, Italy) and **VIT Formula™** (GUNA S.p.a. Milan, Italy) for a period of four weeks, subjectively evaluated by means of a clinical diary (patient diary) designed specifically for the purpose.

70 subjects were identified and enrolled at a first screening visit at T0 according to the protocol's eligibility criteria (Table 2). Only subjects who signed the informed consent form were recruited in the study. During the first visit, the subjects enrolled in the study were administered the Rey's 15-item memory test (Table 3) and the visual-spatial tests of Raven's advanced progressive matrices (examples in Figure 2). At the end of the tests, patients were given the patient diary (Table 4) and the treatment products.

Four weeks later, all the subjects had the T2 check-up visit to assess the same items and collect the patient diary; during this visit subjects repeated the Rey's test and the Raven tests.

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

	Versions:		**Immediate recall**					**Deferred recall**
	Primary	Parallel	**1**	**2**	**3**	**4**	**5**	**After 15 mins.**
1	Curtain	Fireplace						
2	Drum	Trumpet						
3	Coffee	Bread						
4	Belt	Handle						
5	Sun	Bed						
6	Garden	Page						
7	Moustache	Coin						
8	Window	Newspaper						
9	River	Evening						
10	Villager	Carrot						
11	Colour	Mountain						
12	Turkey	Lamp						
13	School	Hotel						
14	House	Man						
15	Hat	Wagon						
	Total							___/ 15

Instructions:

- *"I will read you a list of words, when I have finished, repeat as many words you can remember"*
- The examiner reads one word every two seconds, then asks the patient to repeat as many words that he/she has just heard as possible.
- The word list is repeated 5 times, then after 15 minutes (during which the visual-spatial tests are performed) the patient is asked to repeat the words he/she remembers.
- The primary version (first list of words) will be read to the patient at T0 and the parallel version at time T2.

Table 3. List of words and rules for the administration of the 15-item Rey memory test.

Treatment protocol

Trial treatment was as follows:

- **Tonicoguna (5 g soluble sachets):** 1 sachet dissolved in water to be taken between 8:00 and 10:00 each morning for 4 consecutive weeks;

- **VIT Formula™ (2.5 g orosoluble sachets)**: 1 sachet to be taken via the sublingual route before a main meal every day for 4 consecutive weeks.

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 4).

The data collected during the period of treatment with Tonicoguna and VIT Formula™ were processed by assigning each parameter a numerical score obtained by converting the diary's symptom scale and indicating the frequency with which the specific episode occurred. The data was statistically analysed to assess its significance. The overall analysis of the parameters measured showed a significant improvement in the chronic HPA axis activation syndrome with a considerable reduction in both physical and psychophysical symptoms. Mnemonic-cognitive ability assessment using the Rey test revealed a slight, statistically significant improvement in this function.

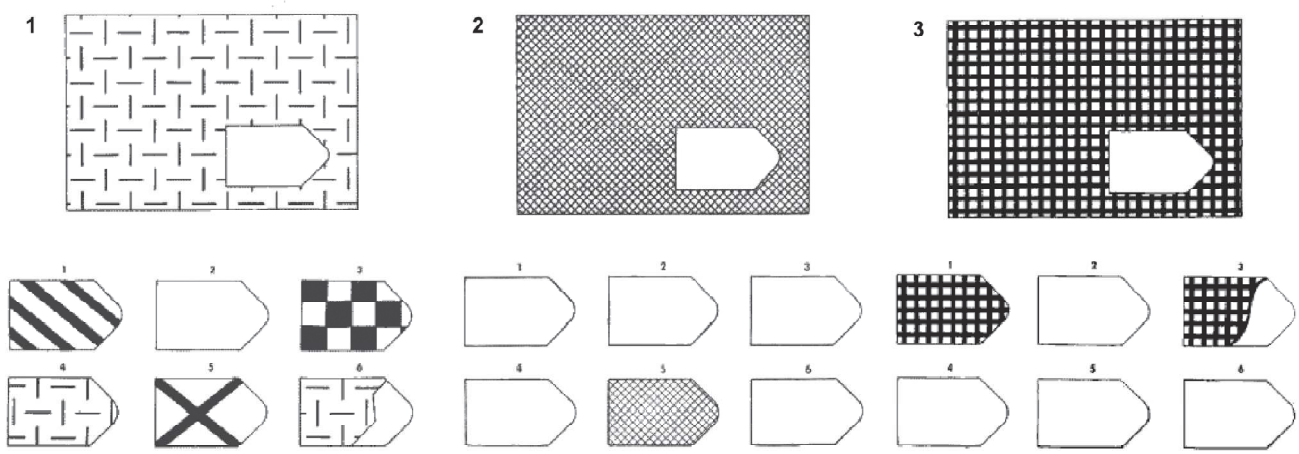

Figure 2: examples of Raven matrices. Raven matrices, also known as progressive matrices, are used to measure non-verbal intelligence. On each sheet the subject is asked to complete a series of figures by choosing the right square from the 6 available. The matrices are administered in order of increasing difficulty, requiring ever keener abilities of item analysis, classification, interpretation and understanding. Raven's progressive matrices are considered the test of election for measuring the intelligence factor *gf*, also known as "fluid" intelligence.

- **Headache**

The score associated with headache episodes tends to drop significantly between T0 and T2 (**ΔT0-T2= -25.46%;** Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1 and between T0 and T2, whereas the difference between T1 and T2 is not significant (figure 3A).

- **Concentration difficulties**

Concentration difficulties undergo a significant improvement: the score tends to drop significantly between T0 and T2 (**ΔT0-T2= -41.76%;** Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1, between T0 and T2, and between T1 and T2 (figure 3B).

- **Memory disorders**

The score associated with memory problems tends to drop significantly between T0 and T2 (**ΔT0-T2= -36.65%;** Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1, between T0 and T2 and between T1 and T2 (figure 3C).

- **Sleep disorders**

The episodes of sleep-wake cycle alterations drop significantly between T0 and T2 (**ΔT0-T2= -27.95%;** test di Friedman: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1, between T0 and T2, and between T1 and T2 (figure 3D).

- **Feeling of psycho-physical exhaustion**

The score associated with the state of psychophysical exhaustion tends to drop significantly between T0 and T2 (**ΔT0-T2= -41.73%**; Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1, between T0 and T2, and between T1 and T2 (figure 4A).

- **Loss of physical strength**

Physical strength shows considerable recovery: the score drops significantly between T0 and T2 (**ΔT0-T2= -43.77%**; Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1, between T0 and T2 and between T1 and T2 (figure 4B).

- **Fatigue**

The score associated with chronic fatigue tends to drop significantly between T0 and T2 (**ΔT0-T2= -43.56%;** Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1, between T0 and T2 and between T1 and T2 (figure 4C).

- **Susceptibility to infection**

Immune system depression causes a greater susceptibility to infection: the score associated with this important parameter drops significantly between T0 and T2 (**ΔT0-T2= -30.99%;** Friedman test: $p < 0.00001$), the Conover test shows a significant difference between T0 and T1 and between T0 and T2, but not between T1 and T2 (figure 4D).

Multicentre observational study on the activity of *Tonicoguna* and *VIT Formula*™ in supporting HPA axis function **PATIENT DIARY**			
PATIENT'S INITIALS:			
DATE OF BIRTH:			
TELEPHONE NUMBER:			
Diagnosis:			
SYMPTOM TREND Use the scale (+), (++), (+++), (++++) to indicate the severity of your symptoms: (+) = **NO** symptoms (++) = **MILD** symptoms (+++) = **MODERATE** symptoms (++++) = **SEVERE** symptoms			
SYMPTOMS	**BEFORE TREATMENT**	**TWO WEEKS AFTER THE START OF TREATMENT**	**FOUR WEEKS AFTER THE START OF TREATMENT**
Feeling of tiredness			
Feeling of psycho-physical exhaustion			
Reduced physical and mental strength			
Sleep disorders			
Memory disorders			
Concentration difficulties			
Headache			
Susceptibility to infection			
Patient's acceptance and appreciation of the product: *(tick as appropriate)*		POOR	
		SATISFACTORY	
		EXCELLENT	
Adverse reactions:		**YES**	**NO**
If so, which: ……			
I hereby authorise the handling of my personal data pursuant to Legislative Decree no. 196 of 2003			
Patient's signature. ……			

Table 4: Patient diary designed for the assessment of symptoms in the TONICOBSERV study

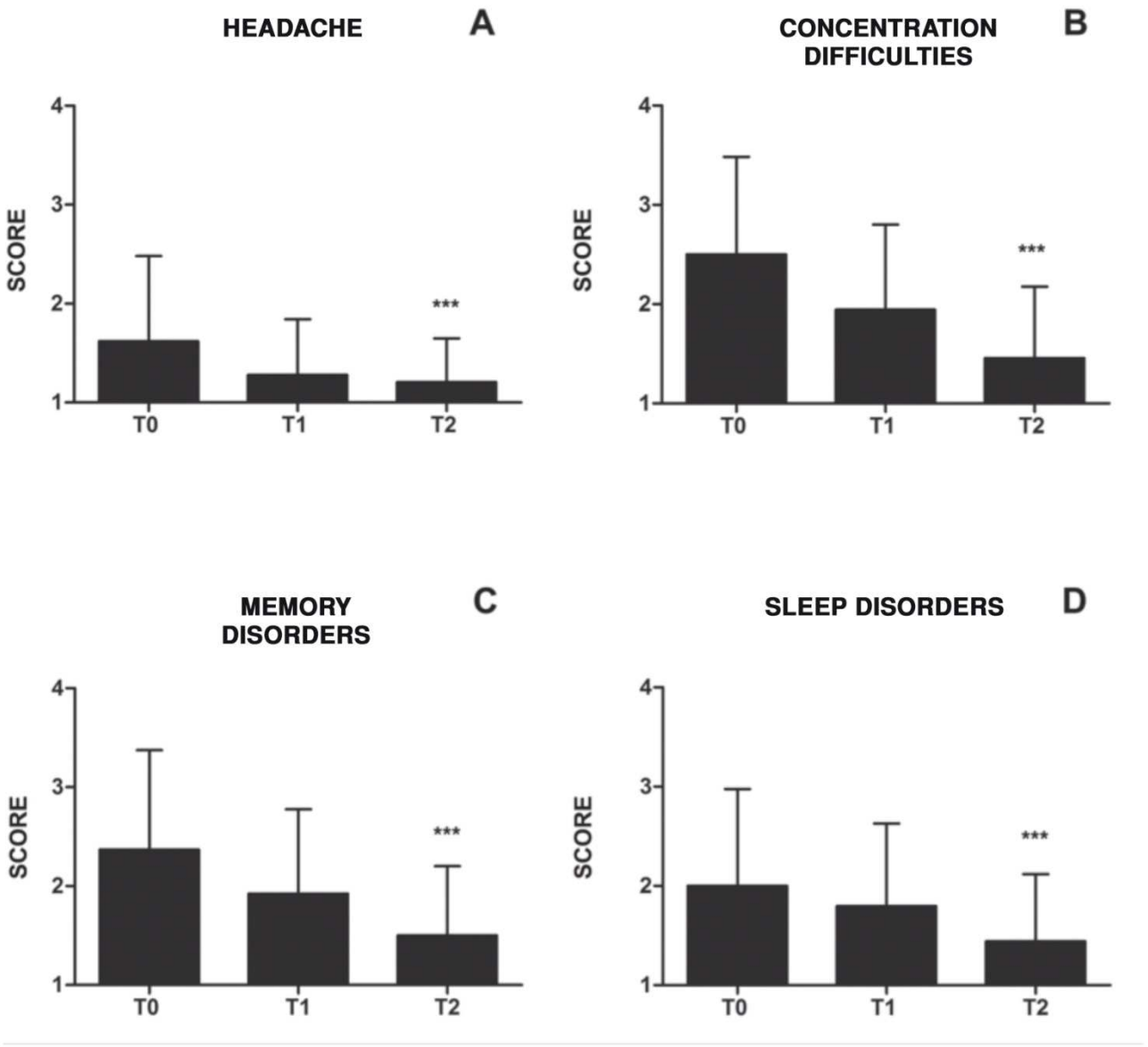

Figure 3: graph showing the distribution of the scores relating to the parameters headache (**A**); concentration difficulties (**B**); memory difficulties (**C**) and sleeping disorders (**D**). All parameters improve significantly following use of Tonicoguna and VIT Formula™.

• **Sum of the Rey test (immediate and deferred recall)**
The sum of the immediate recall Rey test scores rises significantly between T0 and T2 (**ΔT0-T2= +4.71%;** Student's paired t-test: p = 0.0328) (figure 5A). The sum of the deferred recall Rey test scores rises significantly between T0 and T2 (**ΔT0-T2= +8.44%;** Student's paired t-test: p = 0.0035) (figure 5B).

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 products' safety and use according to the protocol.

Discussion
The TONICOBSERV observational clinical study was conducted in order to evaluate the efficacy of the dietary supplements Tonicoguna and VIT Formula™ as treatment for the symptoms associated with chronic stress and consequent appearance of chronic fatigue syndrome (CFS), secondary to HPS-axis desynchronisation.
The results obtained during the TONICOBSERV study show that, in cases of chronic stress associated with CFS, the use of Tonicoguna and VIT Formula™ effectively significantly reduces the symptoms examined. All the parameters monitored showed a significant improvement, thereby proving the efficacy of the treatment; the reduction in the frequency with which the disorders present varies from a minimum of **-25.46%** (headache) to a maximum of **-43.77%** (episodes of loss of physical strength).
Statistical analysis shows that a significant reduction in the symptoms typical of CFS takes place as early as two weeks after the start of treatment with Tonicoguna and VIT Formula™.

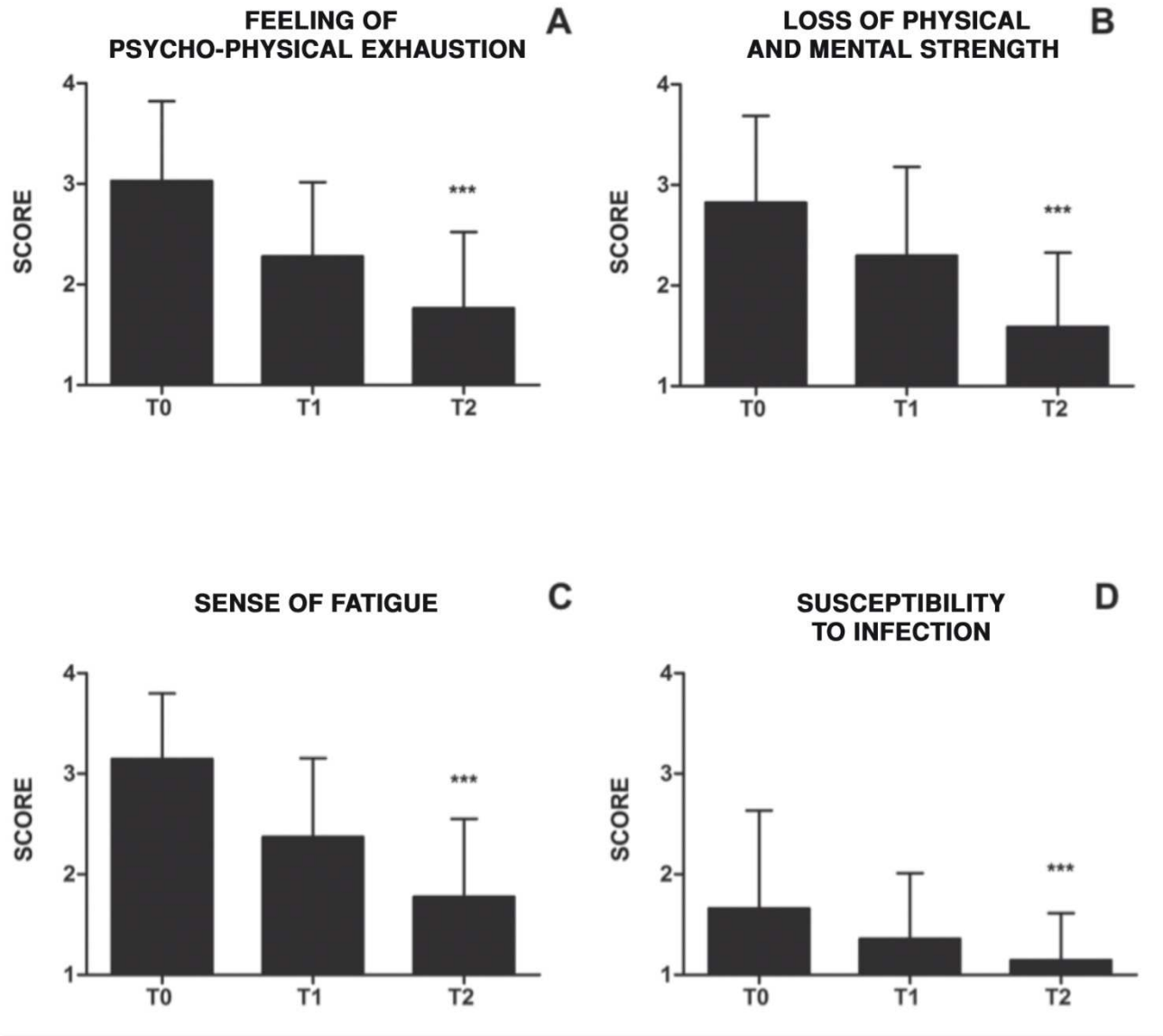

Figure 4: graph showing the distribution of the scores for the parameters: feeling of psycho-physical exhaustion (**A**); loss of physical and mental strength (**B**); sense of fatigue (**C**) and susceptibility to infection (**D**). All parameters improve significantly following use of Tonicoguna and VIT Formula™.

Tonicoguna is a supplement containing plant ingredients developed to support the body in situations of weakness, asthenia, psycho-physical exhaustion, convalescence and stress. The active ingredients of Tonicoguna act in a synergetic and complementary manner by stimulating the entire PNEI axis altered by chronic stress. Tonicoguna's broad-spectrum stimulation action is boosted by the individual actions of the various plant extracts, each of which with specific organic tropism and action (Tables 5 – 6).
Among the ingredients of Tonicoguna, the juice of *Morinda Citrifolia* (Noni fruit) makes up approximately 33% of the formulation and is the most active in reducing mnemonic-cognitive function alterations, by protecting the brain against the damage caused by oxidative stress and against reductions in the vascular density in the hippocampus' dentate gyrus caused by chronic stress (26-28).
VIT Formula™ is a dietary supplement containing a full pool of vitamins (vitamins A, C, D, E, H, PP and K, B group vitamins and folic acid), minerals (iron, calcium, magnesium, zinc, manganese, copper, fluorine, iodine and selenium) and trace elements (methionine, choline and inositol) in balanced quantities for the body and in the most bioavailable form; these elements are vital for optimum body function as they regulate a number of

enzyme reactions. Correct enzyme and protein synthesis system activity is essential for the restoration of homeostasis in the presence of factors of chronic stress.

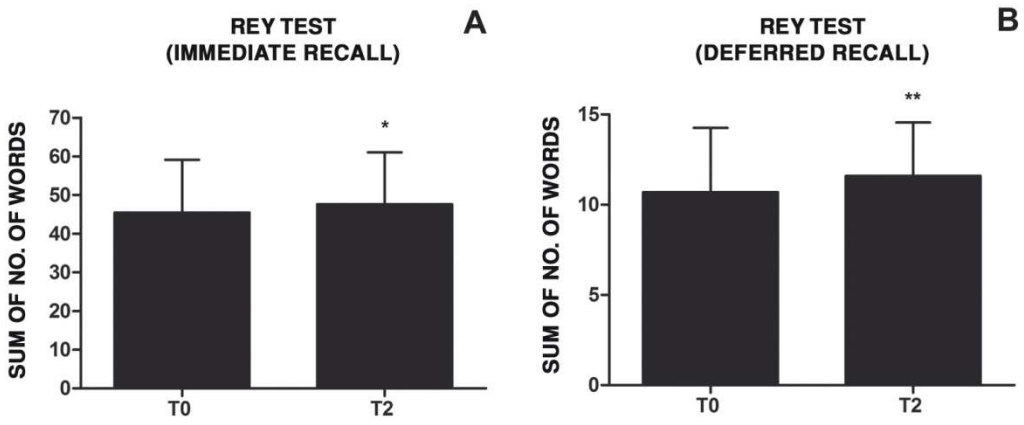

Figure 5: graph showing the results of the immediate (**A**) and deferred (**B**) recall Rey test: treatment with Tonicoguna and VIT Formula™ leads to an improvement in the memory abilities evaluated by the test.

Plant extract	**Main organic tropism**	**Action**
Morinda citrifolia (Noni)	Cell	Anti-asthenic, anti-stress, anti-ageing through stimulation of cell metabolism
Eleutherococcus senticosus	Adrenal glands	Anti-stress, anti-hypnotic, anti-fatigue, general mood stimulation, increase in mental efficiency
Ginkgo biloba	Cell membranes, lesser circulation, adrenal glands	Anti-oxidant, anti-ageing, adrenergic activity, increase in mental efficiency
Ginseng	Anterior pituitary	Hormonal re-balance, adrenal stimulation, increase in mental efficiency
Ribes nigrum	Adrenal glands and immune system	Anti-asthenic, immunomodulating
Hypericum perforatum	Central nervous system	Anti-depressant through I-MAO-like activity
Gentiana lutea	Digestive system	Stimulation of the appetite because of reflex action on the taste buds with increased gastric and salivary secretion
Rosmarinus officinalis	Digestive system, adrenal glands and central nervous system	Nerve stimulation, improved mnemonic and cognitive abilities, anti-ageing activity
Melissa officinalis	Central nervous system	Antidepressant

Table 5: summary of the plant substances present in Tonicoguna and corresponding cell and organ tropism.

TONICOGUNA	**VIT Formula™**
Ingredients: Maltodextrin, Noni (*Morinda citrifolia*) powdered juice, Eleuterococcus (*Eleutherococcus senticosus*) root dry extract (saponin cont. 5%), Flavouring, Blueberry (*Ribes nigrum*) leaves dry extract., Rosemary (*Rosmarinus officinalis*) leaves dry extract, acidity corrector: Citric acid; Hypericum (*Hypericum perforatum*) grass and flowers dry extract (hypericin cont. 0.003%) (hyperforin/hypericin ratio no higher than 7), Gentian (*Gentiana lutea*) root dry extract, *Ginkgo biloba* leaves dry extract (gingko-flavon-glucoside cont. 24%, terpenlactone cont. 6%, Ginseng (*Panax ginseng*) root dry extract (ginsenosides cont. 10%), Melissa (*Melissa officinalis*) leaves dry extract (rosmarinic acid cont. 2%), sweetener: sucralose.	Ingredients: Choline bitartrate 150 mg, calcium carbonate 150 mg, inositol 130 mg, magnesium oxide 75 mg, anti-caking agent: talc; sucrose, flavourings, L-methionin 60 mg, L-ascorbic acid (vitamin C) 50 mg; acidity corrector: citric acid; zinc citrate 15 mg, maltodextrin, ferrous fumarate 4 mg, nicotinamide (vitamin PP) 4 mg, manganese carbonate 2 mg, DL-alpha-tocopherol acetate (vitamin E) 1.5 mg, calcium D-pantothenate (pantothenic acid) 2.1 mg, retinyl acetate (vitamin A) 0.25 mg, sweetener: sucralose; copper citrate 0.5 mg, riboflavin (vitamin B2) 0.38 mg, cholecalciferol (vitamin D3) 2.5 mg, pyridoxin hydrochloride (vitamin B6) 0.23 mg, phylloquinone (vitamin K1) 35 µg, thiamine mononitrate (vitamin B1) 0.15 mg, cyanocobalamin (vitamin B12) 0.25 µg, sodium fluoride 0.09 mg, potassium iodide 64 µg, sodium selenite 33µg, pteroylmonoglutamic acid (folate) 55 µg, D-biotin (vitamin H) 21 µg; sweetener: sorbitol (of corn origin).

Table 6: composition of the two products used in the TONICOBSERV multicentre observational study.

Conclusions

The data collected during the TONICOBSERV observational study show that the use of the dietary supplements Tonicoguna and VIT Formula™ provides an intake of plant substances that have an active effect on controlling HPA axis functions as well as the vitamins, mineral salts and trace elements needed to restore the enzyme and protein synthesis functions compromised by PNEI homeostasis alteration. This activity allows a significant reduction in the conditions of malaise associated with chronic fatigue syndrome and an improvement in the mnemonic-cognitive functions compromised by prolonged stress conditions.

Tonicoguna and VIT Formula™ boast certain particular aspects such as completeness of the formulation, high availability and synergy of the active ingredients, rapidity of action and capacity to maintain the action over time. Specifically, the presence in Tonicoguna of the juice of *Morinda Citrifolia* in significant quantities (33%) guarantees an efficacious protection of the central nervous system against the oxidative and vascular damage caused by stress, an essential condition for the recovery of PNEI homeostasis.

These characteristics make treatment with the dietary supplements Tonicoguna and VIT Formula™ a qualifying element in the treatment of chronic fatigue as part of combined treatment including psychological counselling, lifestyle improvement (diet and exercise) and relaxation techniques.

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