GUNA®-TONIC

DIETARY SUPPLEMENT

The natural answer to chronic stress syndrome, acute and chronic fatigue

GUNA biotherapeutics

Stress and stress syndrome

The brain has a series of pathways connecting it with the rest of the body represented by the so-called **neuroendocrine axes**. By means of these hormonal circuits, the brain influences all of the activities of the body and, in particular, the **immune and endocrine systems**.
The stress axis is the center of the neuroendocrine circuits and acts as an essential hub for regulating the physiology of the body.

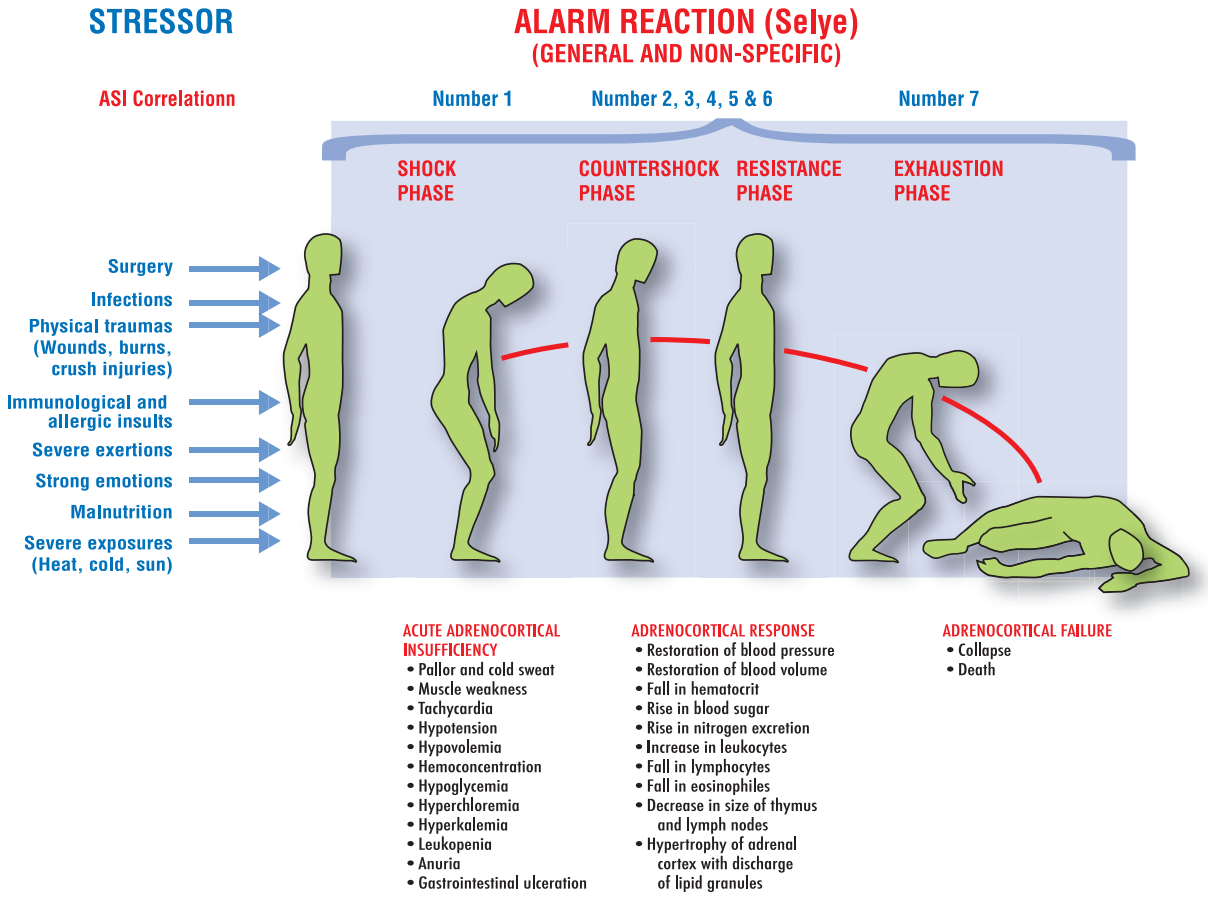
The term "stress" was originally used in engineering to indicate the tension and force to which a rigid material is subjected in conditions of mechanical strain; it was subsequently introduced into biology and has been clearly defined thanks to ***H. Selye***.
In 1936, H. Selye was conducting research to isolate a new sex hormone when he observed that test animals injected with "stressogenic" substances reacted in a similar manner and shared a common syndrome. This syndrome was characterized by **adrenocortical hypertrophy and atrophy of the thymus and lymph glands**.
More recent developments of the concept of stress have led different authors to regard stress as **a broad biological behavioral reaction** aimed at the preservation of life, resulting from a process of natural selection … that is, it is given a **decidedly POSITIVE potency**.
And it must be thus unless the stressor loses its positive potency and acquires a negative potency for various reasons (see below).
When the stressor is not particularly aggressive and the homeostatic control systems are effective, the stress axis is activated in a physiological manner. As Selye observed, the so-called **HPA axis (Hypothalamus-Pituitary-Adrenal Cortex)** is especially activated. This reaction is useful and oriented towards the adaptation of the body to the requirements of its environment.
Conversely, when the stressor is more aggressive or the subject's conditions of homeostatic equilibrium are precarious, **the activation of the stress axis crosses over from physiology to pathology**.

This is the: **"GENERAL ADAPTATION SYNDROME"**, i.e. the sum of all the systemic reactions of the body resulting from prolonged exposure to systemic stress. This syndrome is manifested in **3** successive phases:

- The first is the phase of **ALARM**, with a reaction of acute stress in which the body's defenses are mobilized (pituitary-adrenocortical hyperactivation).

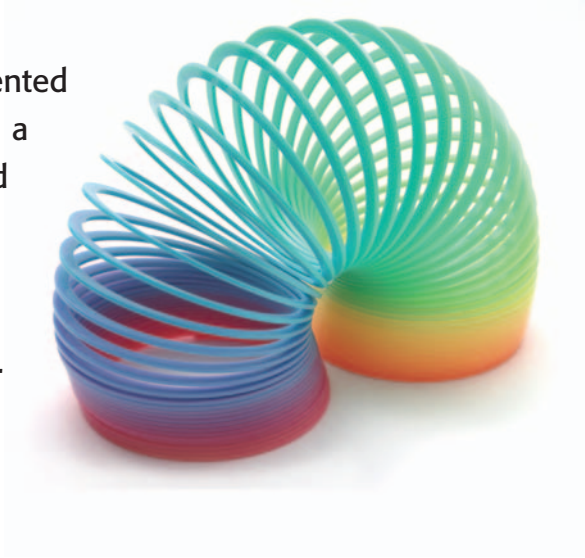
- The second is the phase of **RESISTANCE**, in which the body is required to cope with the stress; the stress reaction is still active and continues the overproduction of cortisol; however, equilibrium starts to alter.

- The third phase of **EXHAUSTION** follows when the exposure to the stress is prolonged in an abnormal manner; **in this phase the adrenal cortex enters a state of functional exhaustion** and pathological conditions are produced that are difficult to reverse, and may even result in death in extreme cases.



With this theory, the existence of a relationship between dangerous external stimuli and the body's internal reaction was established for the first time. Moreover, it was found that the stress reaction was a non-specific type of reaction that was the same towards heterogeneous stimuli. Finally, the significance of the stress reaction was established as a **fundamental, adaptive and defensive reaction of the body, which could, however, in certain cases be the origin of serious disorders**.

The STRESS - STRAIN relationship can be represented schematically by the attachment of a weight to a spring, where the weight represents the load (STRESS) and the lengthening represents the deformation that the spring undergoes (STRAIN). **If the weight exceeds the elastic capacity or the break load of the spring, the deformation becomes irreversible**.



SUMMARY

STRESS SYNDROME has different chemical variants sharing the following characteristics:

- The pathophysiological response is non-specific and so different stimuli can lead to very similar or identical chemical manifestations.
- The course of the disease is uniform and characterized in succession by a first phase of **alarm**, of reaction to the stressors, by a second phase, called the phase of **resistance**, in which the defenses alerted in the first phase are in precarious equilibrium; finally, a third phase of **exhaustion**, in which, while the stressors persist, the defenses are exhausted with subsequent development of a state of functional exhaustion.
- **The mediators of the *stress-strain* reactions are the endocrine system, the autonomic nervous system and the immune system.**

Another essential characteristic of the manifestations of *strain* is the twofold potency, **somatic** and **behavioral**, of the responses to environmental factors so that psychological reactions, somatisation phenomena and integrated psychological responses can occur alternatively:

Behavioral disturbances give rise to a broad range of disorders, including, for instance:

1) *Abuse of alcoholic substances*
2) *Smoking*
3) *Eating disorders (over- or under-eating)*
4) *Generalized inhibition or overexcitement*
5) *Affective-emotional reactions (sadness, irritability, depression, poor concentration etc.)*

Among ***psychological*** and ***physiological*** disturbances, the following are the most important and found with greatest frequency:

1) *Sleep disturbances and drowsiness during the day.*
2) *Poor appetite.*
3) *Asthenia.*
4) *Memory disturbances.*
5) *Amenorrhea (raised levels of CRH, ACTH and cortisol inhibit GN-RH and LH).*
6) *Cardiovascular symptoms: the heart rate and cardiac output increase to provide blood to the regions needed to respond to the stressful situation with resulting subjective symptoms of palpitations (various hormones responsible, especially adrenaline).*
7) *Dyspnea: the respiratory rate increases to provide the oxygen required by the heart, the brain and the active muscles.*
8) *Arterial hypertension: its genesis depends on the type of work, the alteration of the systems involved in its regulation (e.g. central and peripheral nervous system, hormones [adrenaline, glucagon, cortisol], cardiovascular apparatus etc.)*
9) *The digestive function is reduced drastically as it is not important in order to cope with stress.*
10) *Increase in glycemia (through the rise in hormones that are antagonistic to insulin such as cortisol, adrenaline and glucagon and through the release of glucose by the liver).*

11) *Hyperhydrosis: sweating increases to eliminate the toxic substances produced by the body and to lower body temperature.*
12) *Generalized muscle tension associated with psychomotor restlessness and inability to relax. This is all due to the diversion of blood from the skin and from the internal organs (except the heart and lungs), to increase the amount of oxygen and glucose to the muscles and brain.*
13) *Reduction of the immune defenses (the significant relationship between stress and cancer has already been noted) from atrophy of the lymphatic system with conditions of Herpes, colds and influenza type etc.*
14) *Anxiety-depression syndromes: prolonged exposure to cortisol lowers the levels of noradrenaline in the neurons of the locus coeruleus, thus causing a reduced capacity for concentration, alertness, general activity, serotonin and dopamine (thus lowering the sensations of pleasure. On the contrary, when a stress is limited in time, immediate pleasure is experienced).*

"GOOD" STRESS AND NON-OPTIMAL STRESS REACTIONS

In certain conditions, stress can lose its functional adaptive meaning and represent a possible source of risk for physical and/or mental health.
It has been known for centuries, since Greek and Roman medicine, that physical diseases can arise in particular emotional conditions (death of close friends and relatives, serious family problems, work problems etc.).

Stress scale

EVENT	VALUE
Death of spouse	100
Divorce	73
Jail term	63
Personal injury	53
Marriage	50
Fired at work	47
Retirement	45
Pregnancy	40
Sex difficulties	39
Change in financial state	38
Mortgage	31
Sons/daughters leaving their parents' household	29
Troubles with boss	23
Vacation	15
Christmas holidays	13
Minor violation of the law	11

From the 1940s up to today, a significant quantity of clinical and experimental data has been accumulated which has demonstrated with ever-greater clarity that conditions of existential stress associated both with the occurrence of particular life events and with the presence of chronically stressful events can promote the onset of physical diseases.

- **OPTIMAL STRESS** is represented by **conditions of rapid activation and deactivation**, with **stress reactions divided into synchronous and inte-**

grated biological and behavioral responses. In the optimal stress reactions, activation of the involved biological systems and of the responses at behavioral level **are limited in time**, but not activated abnormally and not excessively prolonged. Moreover, it is appropriate that the body is accustomed to the phasic activation required by the stress reaction. Alterations of the ideal characteristics of this condition of optimal stress are of various types and are often those that increase the risk of disease.

- **NON-OPTIMAL STRESS reactions** include: acute high intensity stress; stress in acute conditions and/or chronic in conditions that block the action; chronic overproduction of stress consisting of a condition in which exposure to the stressor continues over time beyond the body's possibilities for reaction.

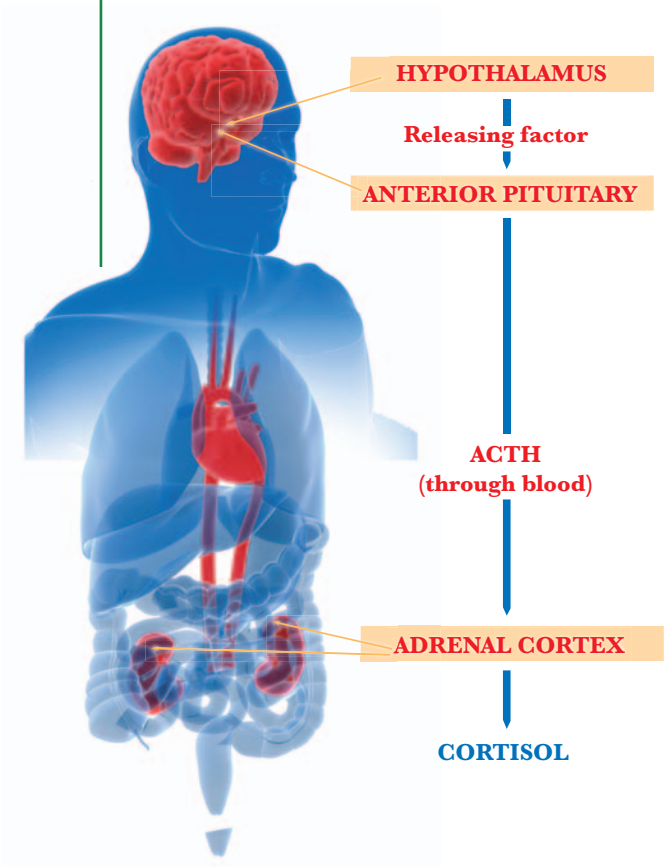
  1. **Acute stress of raised intensity (hyperstress reaction)** is triggered by both physical and psychosocial stimuli and has a predominantly adaptive purpose. Selye had already shown how, in the first phase of the general adaptation response (alarm reaction), it is possible that some manifestations of the stress reaction in acute and particularly intense conditions can be the basis of pathological reactions, especially in organisms that are predisposed or at risk.
  2. **Chronic overproduction of stress** consists of a condition in which exposure to the stressor continues over time beyond the body's capabilities to react. In many aspects, this coincides with the phase of exhaustion described by Selye as the final phase of the general adaptation syndrome. In this phase, the body's capacities and resources for reaction are exhausted after the alarm phase and the resistance phase.

Pathophysiology of stress

ANATOMICAL AND PHYSIOLOGICAL ORGANIZATION

The stress system is organized into two areas: **one chemical (endocrine) and the other nervous**.

The **CHEMICAL AREA** starts from the hypothalamus which, as we know, is an area of the brain organized into nuclei. **CRH** (a hormone that releases corticotropin) and AVP (arginine vasopressin) are released by the neurons of the paraventricular nuclei (which are therefore located around the third cerebral ventricle).



These substances stimulate the pituitary to produce **ACTH** (adrenocorticotropic hormone).

Unlike CRH, AVP on its own is not a potent pituitary stimulator but it becomes one in synergy with CRH. The connection between the two is suggested by the fact that there is a population of neurons of the parvocellular group, which produces the two molecules together: these "dual production" neurons multiply under stress, thus increasing the degree of pituitary stimulation.

ACTH released by the pituitary reaches the adrenal cortex through the blood stream, where **cortisol** is released from the intermediate layer (the "zona fasciculata").

*The chemical area is therefore also defined as the **hypothalamus-pituitary-adrenal axis**.*

The principal effects of **stress hypercortisolemia**:

a) Effects on **gluconeogenesis**: hepatic gluconeogenesis is stimulated with a large resulting rise in glycogen in the liver cells.

b) It diminishes glucose utilization by the cells. The result of the two points "a" and "b" is **an increase in glycemia**.

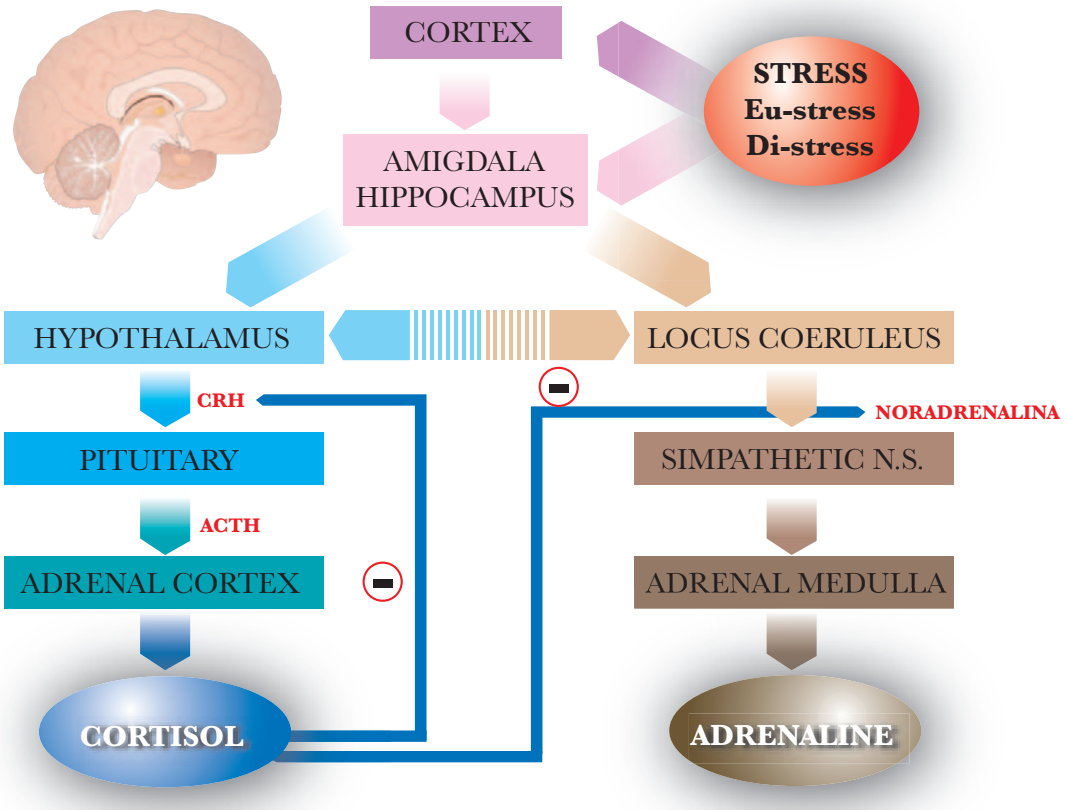
c) It reduces protein synthesis and increases the catabolism of proteins already produced within the cells. Thus, if the cortisol levels are too high, **immune functions can be greatly depressed and the subject's muscles can become weakened**.

d) It mobilizes fatty acids from adipose tissue and increases their oxidation. In the event of stress, this alters cell metabolism which no longer utilizes glucose for energy purposes but **increases the production of fatty acids**.

e) **Obesity due to cortisol**: many patients with hypersecretion of this hormone have a particular type of obesity (buffalo hump trunk, moon phases), which is caused by an excessive urge to consume foods from which fat is produced at a faster rate than it is metabolized in certain regions of the body.

f) Effects on the immune system. In chronic stress, there is a **reduction of immune defenses** since cortisol causes a reduction in the lymphocytes and eosinophils in the blood. If its action is prolonged, this induces major atrophy of all of the body's lymphoid tissue and this in turn causes a reduction in the production of T lymphocytes and antibodies by this tissue.

g) According to many studies, there is a significant relationship between destructive stress (which consists in major aggressiveness that is not expressed or discharged to the exterior) and **cancer**.



The **NERVOUS AREA** is organized as follows. The parvocellular hypothalamic nuclei are closely linked by bands of nerve fibers to nuclei located in the first part of the **spinal cord**, and in the area of the *pons and medulla*. These nuclei define an area known as the **locus coeruleus, which produces noradrenaline in particular**. The locus coeruleus and the parvocellular hypothalamic nuclei are reciprocally linked in that bands of nerve fibers enter and leave the two areas.

A signal thus starts from the locus coeruleus which, **through the sympathetic nervous system**, is able to stimulate the inner part of the adrenals, known as the adrenal medulla, to produce a mixture of **excitatory substances: adrenaline, noradrenaline and dopamine (catecholamines)**, in variable amounts in decreasing order. The adrenal medulla is able to produce neurotransmitters due to the fact that it contains a population of cells, known as chromaffin cells, which have the same embryological origin as nerve tissue.

Thus, to sum up, a chemical signal starts from the paraventricular nuclei of the hypothalamus, which passes through the pituitary and adrenal cortex with the final outcome of cortisol production. At the same time, a nerve signal is activated which passes through the locus coeruleus and the sympathetic nervous system to produce release of catecholamines by the adrenal medulla. The unity of the stress system is due to the fact that the hypothalamic CRH and the noradrenaline produced by the *locus coeruleus* stimulate each other reciprocally.

The hypothalamus-pituitary-adrenal axis is self-regulating (negative feedback) in that the circulating levels of cortisol are read by the hypothalamus and also by the pituitary through specific receptors, which thus allow activation or inhibition of the system according to the circulating levels of cortisol.

This is the reason why, in the syndrome of chronic stress, the continuous secretion of cortisol induces the hypothalamic non-response and thus the condition of "surrender" of the body to stimuli that should necessitate a response. This is why there are symptoms of fatigue, asthenia, poor interest in life etc.

CHRONIC STRESS SYNDROME: SYMPTOMS

Frequent general fatigue	Back pain
Colitis	Restlessness and agitation
Irritable Colon Syndrome	Tic (face, eyes, mouth)
Stomach ulcer	Dry mouth
Hypertension	Shivering
Irregular heartbeats (arrhythmia)	Excessive sweating
Asthma or irregular breathing	Pain and a hollow feeling in one's stomach
Migraine, headache	
Muscle pain	Bad digestion
Need to urinate frequently	Nausea
Change in the voice (usually acute voice)	Sleep disorders
	Changeable mood
Immune system weakening	Sex difficulties

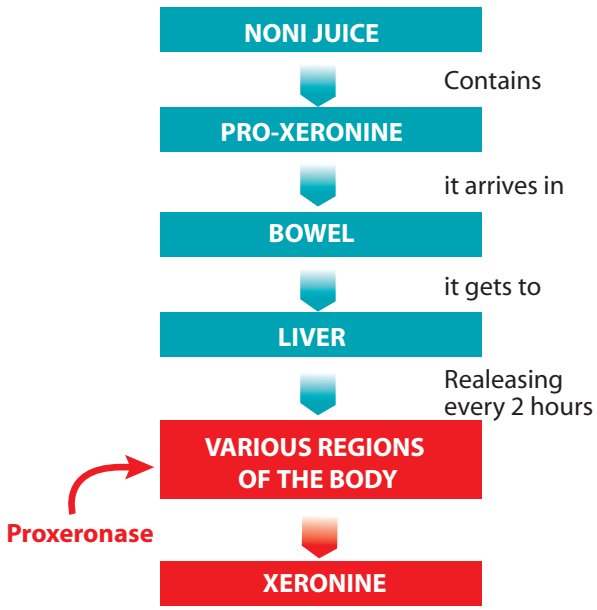
GUNA®-TONIC

Dietary supplement

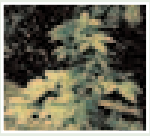
Technical data

Guna-Tonic resulted from the encounter between Polynesian and European knowledge of phytotherapy, a modern and innovative integrator based on plant principles, designed to support the body in situations of weakness, asthenia, mental and physical exhaustion, convalescence, stress and, in general, in all conditions where **energy** and **drive** are necessary.
Guna-Tonic contains a pool of plant extracts selected for their well-known **fortifying, stimulating and energizing properties**.
Prominent among the ingredients is *Morinda Citrifolia* extract; a Polynesian plant better known by the name *Noni*, which has been used for centuries by the peoples of the South Pacific to treat a wide range of diseases. The 100% pure juice is high in vitamins, minerals, amino acids, enzymes, trace elements, sterols and xeronin, substances with a tonic, antioxidant, immunostimulant, antibacterial and analgesic action. Advanced scientific clinical study has demonstrated the therapeutic qualities of this plant. Its properties are known traditionally and have been confirmed by recent scientific study.
The other plant ingredients potentiate the peculiar effects of the **Noni juice** and together constitute the synergistic elements of a complete, natural and effective supplementation.

NONI PHARMACODYNAMIC FLOW CHART



XERONINE: is a superenzyme metabolic co-regulator with several actions:
PROTEIN SYNTHESIS
METABOLISM STIMULATION
CELL MITOSIS STIMULATION

	Plant extract	Main organic tropism	Action
	Morinda citrifolia *Noni*	Cell	Anti-asthenic, anti-stress, anti-aging by stimulating cell metabolism.
	***Russian ginseng*** *Eleutherococcus senticosus*	Adrenal glands	Anti-stress, anti-hypnotic, anti-fatigue; stimulation of general tone, increase in mental efficiency.
	***Ginkgo*** *Ginkgo biloba*	Cell membranes, microcirculation, adrenal glands	Antioxidant, anti-aging, adrenergic activity; increase in mental efficiency.
	***Ginseng*** *Panax ginseng*	Anterior pituitary	Hormonal rebalancing, adrenal stimulation, increase in mental efficiency.
	***Black currant*** *Ribes nigrum*	Adrenal glands and immune system	Anti-asthenic, immunomodulating.
	***Goatweed*** *Hypericum perforatum*	Central nervous system	Antidepressant.
	***Great yellow gentian*** *Gentiana lutea*	Digestive system	Appetite stimulation by reflex action on the taste buds with an increase in gastric and salivary secretion.
	***Rosemary*** *Rosmarinus officinalis*	Digestive system, adrenal glands and central nervous system	Nerve stimulation, potentiation of memory and cognitive faculties, anti-aging activity.
	***Lemon balm*** *Melissa officinalis*	Central nervous system	Antidepressant.

GUNA-TONIC

Ingredients

Noni (Morinda citrifolia) fruit juice, Siberian Ginseng (Eleutherococcus senticosus) root, Black currant (Ribes nigrum) leaf, Rosemary (Rosmarinus officinalis) leaf, Great yellow gentian (Gentiana lutea) root, Ginkgo(Ginkgo biloba) leaf, Ginseng (Panax ginseng) root, Goatweed (Hypericum perforatum) flower Lemon balm (Melissa officinalis) leaf, Orange (Citrus aurantium) fruit juice.
Other ingredients: Water, Fructose syrup, Orange natural flavoring, Hydroxypropyl methylcellulose, Preservative: Stabilan®. Alcohol content: 7 % v/v

Directions

Guna-Tonic is a dietary supplement formulated to strengthen and stimulate the body's natural defenses in **conditions of stress**. It is used as a support for daily activities as a **source of energy and natural well being**.
Its antioxidant, immunostimulant and tonic effects make it an excellent support for **improving mental efficiency**, **concentration and school or work performance**, **optimizing sporting performance**, **aiding digestive processes** and, in general, **in all situations of weakness**, **mental and physical exhaustion**, **convalescence and stress** where energy and drive are necessary.

Raccomanded use

Take 20 ml per day in a single dose (preferably in the morning) or in two doses, using the special measuring cap. It may be diluted in a little water.
It is advisable to take Guna-Tonic at 9 a.m. and at 3 p.m. because these hours coincide with the maximum pulsatile activity of the adrenals.
Oral solution, free of saccharose, glucose, lactose and gluten.

Warnings and contraindications

It contains Gingko biloba; that may interfere with anticoagulants if you are taking anticoagulant drugs or antiplatelet drugs, consult your doctor before taking this product.
During pregnancy and when breast-feeding, consult your doctor.
The daily dose contains 2.6 mcg of hypericin.

Note

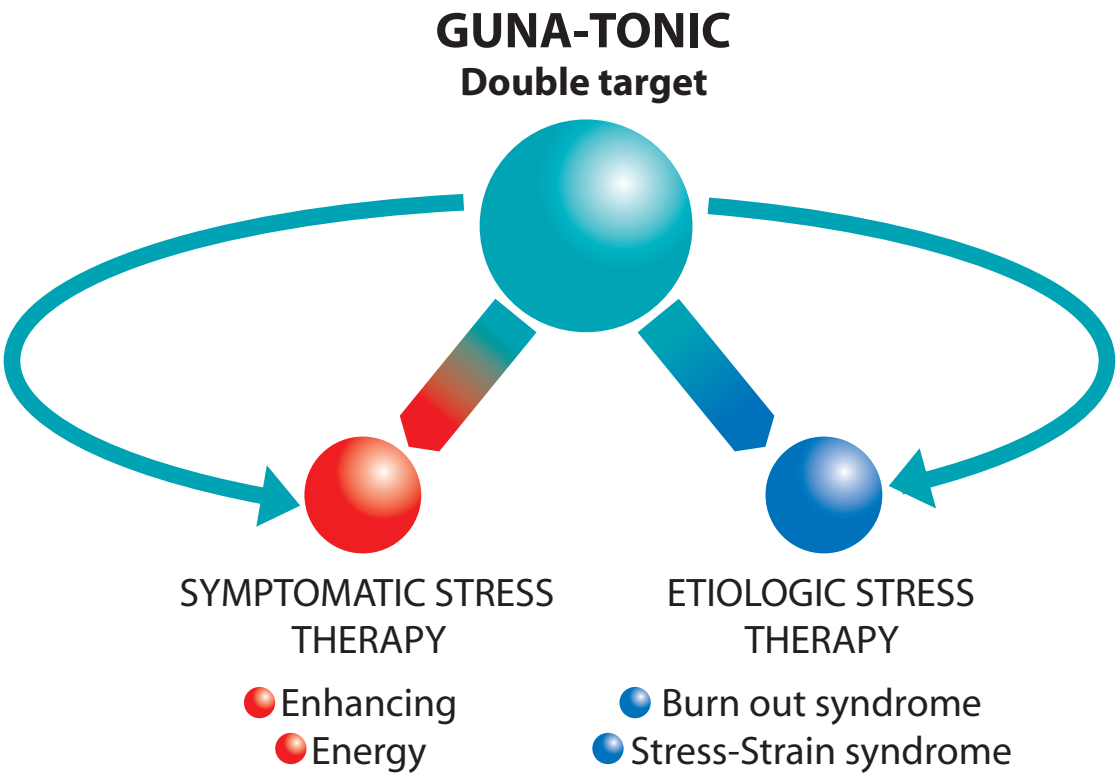
Noni juice (fruit of Morinda Citrifolia) complies with
Directive (CE) 258/97 and is of guaranteed origin from Tahiti.

Packaging

PET bottle containing 150 ml with safety cap and dosing measure.

Guna-Tonic target:

Syndromes of debilitation, asthenia, chronic fatigue, mental and physical exhaustion, convalescence, stress, loss of appetite, mental strain (school, work commitments etc.).



SCIENTIFIC PRESENTATION

The **main target** of Guna-Tonic components, apart from Noni, which works on cellular enzymes, are the adrenal glands, which are stimulated gently by *Eleutherococcus*, *Ginkgo biloba*, *Ribes nigrum* and *Rosmarinus*. These latter elements can be regarded as **tonics for the adrenals, so they are ideal in conditions of exhaustion typical of chronic stress situations**.
Another qualifying aspect of Guna-Tonic is the characteristic of synergizing and complementary action of its components which is fundamental in order for it to have a real effect on a syndrome such as **chronic stress and burn out**; this can be regarded as a problem of **desynchronization** of the stress axis, on which we can act only at a global level, both on the pituitary (*Ginseng*), the adrenals (see above), and the CNS (*Hypericum*, *Melissa*).
It is also highly interesting to consider the components of Guna-Tonic **in terms of energy**. For instance, the ingredient of *Rosmarinus* stimulates the draining and energy function of the liver and according to the Traditional Chinese Medicine "decongests" the yang kidney (the adrenal) and tones the yin kidney (the true kidney, "root" of energy).

So we can say that the use of Guna-Tonic is twofold:
On the one hand, Guna-Tonic is indicated for acute **conditions of asthenia and fatigue** because of its adrenergic action; on the other hand, it is an ideal product for **burn out syndrome** as it resynchronizes, at a global level, the axis that has been altered by stress.