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# THERAPY OF THE EXTRACELLULAR MATRIX INTOXICATION WITH PHYSIOLOGICAL REGULATING MEDICINE


## SUMMARY

**The extracellular matrix (ECM) represents and "forms" the ground system of all living beings, a locus where nourishment, control and management of all cells are concentrated and a mutual exchange of information (molecules-energy) takes place.**
**From the organoleptic point of view, ECM is a sol-gel gangue composed of glycosaminoglycans (GAGs) = heteropolysaccharides patterned in repeated helical disaccharide unities. They are highly hydrophilic, viscous, negatively charged, perpendicularly gathering around a protein core. The combination of many GAGs units with a protein forms a proteoglycan (PG), giving the macromolecule a typical "brush-filter" shape.**
**The role of the free and linked (PGs) GAGs ensure homeostasis: isoionicity, isosmoticity, isotonia. Moreover, the ECM is composed of self-assembly collagen, elastin, reticular glycoproteins, fibronectin, laminin, vitronectin, thrombospondin, tenascin, lectins - all of them immunogen mediators.**
**An electromagnetic signal picked up by the glycocalyx and its endocellular extension loses little energy. In the ECM, the electromagnetic wave closes upon itself, becoming a photon and regaining its undulatory character when it moves to the cytoplasm. As soon as the catabolic, environmental, food pathogen toxic agents pollute the glycocalyx, the $H_2O$ molecules change their dielectric constant: the electromagnetic-signal waves do not become photons and, as not being recognized by the calyx proteins, trigger counter-response-pathology mechanisms. Every human carries one or more than one genetic change concerning the complex biosynthesis of the GAGs and PGs molecules but these do not become macroscopically phenotypes. During one's lifetime, catabolites are stored up making energy exchanges from and towards cells difficult. Thanks to Trincher's principle (biological time x Delta T = constant), every cell lives a finite time.**

**- One of the most effective PRM medical product to clean up and restore the complex role of the ECM is undoubtedly GUNA®-MATRIX. In this paper, GUNA®-MATRIX is analyzed and discussed on the basis of current scientific updates.**


KEY WORDS **PROTEOGLYCANS (PGS), ESOSAMINOGLYCANS (GAGS), PHYSIOLOGICAL REGULATING MEDICINE, GUNA®-MATRIX**

## INTRODUCTION

The matrix is a fundamental extracellular (ECM), pericellular and intracellular substance for metabolic interaction, a ubiquitous tissue characterized by physiological SOL-GEL synchronicity. The current unitary view of the matrix overlooks neither the morphological and biochemical aspects of its constituents, nor the general biological aspects in which it operates in a phylo- and ontogenetic unity that sees current living beings as the last surviving witnesses which have filtered through the mesh of evolution. In this publication, the amorphous extracellular structures of the matrix (interstitial matrix) are primarily considered; the author considered the cellular aspects in a previous publication [Milani, 2003 (c)].

- The most important stages in the evolution of organisms - when organized into tissues - were accomplished in the final detailing of the structural genes as well as the biosynthesis control of the matrix constituents.

Hyaluronic acid is phylogenetically the earliest glycosaminoglycan (GAG). It does not involve any nucleic acids. It is a biological *fossil*, the first component of the matrix that appears during the development of the mesenchyme from the 2nd week of human embryonic development. It is not only present in the first phases of the constitution of life but also in the very first phases of the constitution of a new life: the spermatozoon enters the ovocyte thanks to hyaluronidase. The molecular structure of the proteoglycans (PGs) is very conservative: it maintains the same form in all pluricellular organisms. PGs and GAGs are present only in the animal kingdom.

The sugar structure is not DNA-encoded like the amino acid sequences, for which the matrix enjoys great adaptability through autocatalysis.

The Virchow paradigm (1862), which regards the cell as an "elementary organism", was made obsolete by Pischinger (1979), who not only suggested a change of polarity of current thinking but also pointed out the sense and the purpose of the single parts interacting with the whole working system: terms such

as "synchronicity", "synergy", "biological unity", revive and detail the reductive principle of feed-back, thus altering it; the purely mechanistic concept of feed-back must be replaced by the more elastic concept of intra-relationship and inter-relationship between parts understood not as "bricks in a single wall" but rather as a "wall *in toto*".
The task of science is to focus on the details of reality, anatomizing and describing them meticulously, but without forgetting to reassemble them as far as possible; from this operation, the substantial facts of the integrated vision of the Physiological Regulating Medicine emerge and stand out: the total is more than the sum of its parts.
This gives the deeper and more subtle meaning to the art of healing.

## ECM

The ECM "represents" and "forms" the basic system of living organisms. It is the locus in which:
1. Nourishment
2. Control
3. Management

of all cells find their own integration and the moment of mutual information exchange (molecule-energy).
The matrix is a chronopatho-dependent extra- (ECM) and pericellular sol-gel gangue consisting of:

### *1) Glucosaminoglycan (GAGs)*

Heteropolysaccharide built according to repetition of disaccharide units (up to 25,000).

Each disaccharide unit consists of:
a) *N-acetylglucosamine* or *N-acetylgalactosamine*
b) Residue of *glucuronic acid* or *iduronic acid* } *uronic acids*

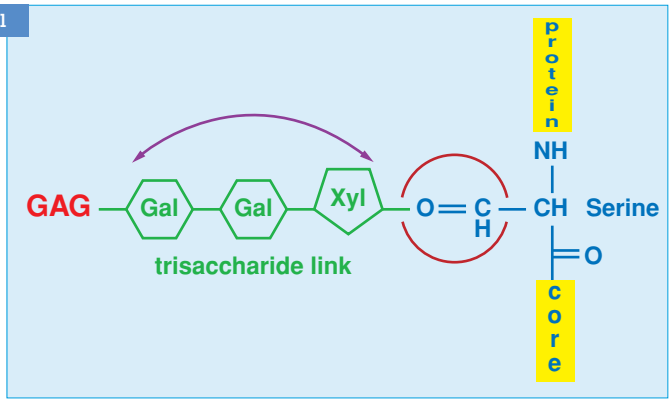
GAGs are characterized by the presence of sulphuric esters which, with the carboxyl groups of the uronic acids, confer on the molecules **a considerable density of negative charges and viscosity**.
Recently, various techniques as X ray crystallography, Circular dichroism, Rotatory optical dispersion, NMR, have revealed that GAGs have a characteristic helicoid-hyperboloid conformation.

Due to their:
- Viscosity: they are the ideal molecules for lubrication (e.g. synovial liquid);
- Rigidity: they are the guarantors of the cellular structural integrity providing the "passages" among cells, thus allowing cellular migration.

Liu and Coll. (2003) have shown how molecular engineering can be used to form different types of ECM to create "permissive niches" in which the CNS progenitor cells can be directed in the required direction.
They have developed 3 different proteins of artificial ECM in which a signal system instructs the neuronal progenitor to "choose" the or a glial destination.
In actual fact, the GAGs relax the chromatin structure and make it easy for the polymerases to "read" DNA.

FIG. 1

**Orthogonal fixation of a GAG to a protein core**




### *2) Proteoglycans (PGs)*

The GAGs are perpendicularly bound to a protein (protein core) through a trisaccharide link and an O=CH bond (FIG. 1).
The point of attack consists of a -S residue. The form of a proteoglycan is that of a brush-filter (FIG. 2).
Thanks to the polyanionic GAGs of a PG, they can bind H2O, exchange ions, bind cytokines, growth factors, metal ions, catabolites and toxins.
Only hyaluronic acid and heparin (GAGs) are not bound to a protein skeleton, free in the ground substance.
The role of the free and linked (PGs) GAGs ensures homeostasis:
- **Isoionicity**
- **Isosmoticity**
- **Isotonia.**

During human lifetime, the PGs and the elastin start to decrease from the age of 20-25 years, while the collagen increases with a maximum peak at 50 years. These out-of-phase curves are responsible for the structural deterioration of the matrix with important repercussions on the biological vitality of the body.

Their structure varies according to the type and number of the polysaccharide chains of GAGs and according to the amino acid sequences which form the protein support chain (protein core).
Some of these molecules can unite in supramolecular aggregates of very high molecular weight.

The PGs are highly polymeric macromolecules. In the aggrecan of cartilage, 1 g of dry weight can absorb up to 50 ml of $H_2O$.

The $H_2O$ in the matrix, thanks to the fact that the fulcrums of the + and - charges do not coincide, thereby giving it a peculiar polar character, is principally bound to the sugars.

## WATER ANOMALIES

The $H_2O$ is a real liquid, lacking in anomalies upwards of 60°.

Between 0° and 60° it is like a fluid ice with almost crystalline components combined with really liquid components.
These 2 phases are in equilibrium at 37.5° (Franks, 1972; Trincher, 1981).
Through autocatalysis, continuous spontaneous reorganization is obtained in the matrix with:
1) promotion; 2) transfer; 3) information cancellation.

From the moment in the course of life when the GAGs and PGs decrease, a progressive loss of fluid-crystalline $H_2O$ is apparent with loss of the functions 1), 2) and 3).

The proteoglycans (TAB. 1):
1) They participate to a determining measure in the formation of the ECM;
2) They are present on the cell surface;
3) Small PGs are present in the cytoplasm;
4) They are a "bridge" (glycocalyx) between cells and ECM; they cross the cell membrane that can come into contact with the cytoskeleton (microtubules).

The network resulting from these interactions, besides having a supporting role, can regulate the flow of diffusible molecules by acting as a filter, influencing the mechanisms that are found at the level of every single cell.
The large amount of $H_2O$ retained by the PGs gives the tissue elasticity and resistance.
During the aging processes, the PGs go towards a diminution in chondroitin sulphate and an increase in keratan sulphate (highly represented in the ECM) with lesser ability to retain $H_2O$.
These events explain the following:
1 Biological senescence
2) Cutaneous wrinkling
3) Shrinkage in stature
4) Implosion of the organs, especially the parenchymatous organs.
The PGs concentrate around them the counter-ions causing + osmotic pressure on the tissue.
The PGs have high affinity for calcium and they intervene in the processes of calcification.
Other recognized properties:
- Wound repair
- Concentration of the urine in the kidneys
- Accumulation and release of biogenic amine

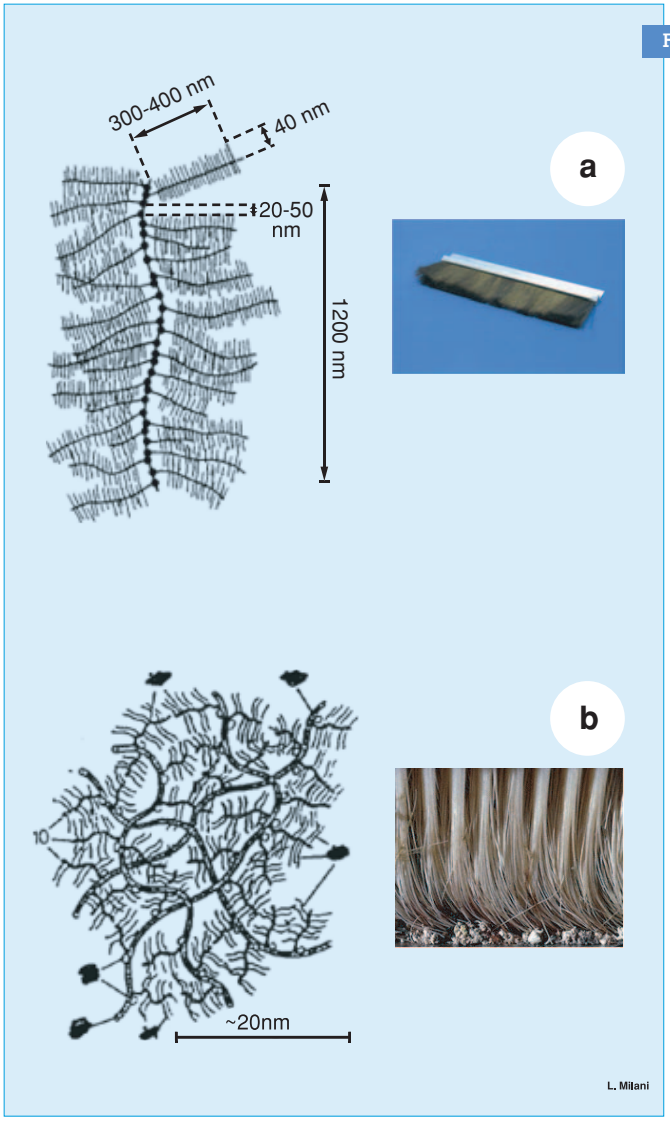



FIG. 2

**ⓐ The structure of a proteoglycan (PG) is comparable to that of a brush: the trisaccharide Galactose-Galactose-Xylose link (Fig. 1) turns like a cardan joint on the group O=CH allowing the glycosaminoglycan (GAG) a certain degree of rotation on itself: from this perspective, a PG runs like a rotating brush;**

**ⓑ Curious morphological and functional analogies among the PGs meshwork of the ECM and the baleens of the cetaceans: as the latter act as a water filter to trap plankton, the former filter the macromolecules to be selectively carried in the cytoplasm.**

TAB. 1

**ECM structure**

| GAG | PG (from 50 to > 2500 Dalton) | |
|---|---|---|
| DERMATAN SULPHATE | Syndecan | → epithelial cell membrane |
| CHONDROITIN SULPHATE | Decorin | → extracellular matrix |
| | Versican | → extracellular matrix, vascular wall |
| | Aggrecan | → cartilage |
| KERATAN SULPHATE | Fibromodulin | → extracellular matrix |
| | Biglycan | → extracellular matrix |
| | Syndecan | → epithelial cell membrane |
| HEPARAN SULPHATE | Perlecan | → basal lamina |
| | Fibroglycan | → fibroblast cell membranes |
| | Glypican | → endothelial, epithelial and smooth muscle cell membranes |
| HYALURONIC ACID | | |
| HEPARIN | | |

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- Regulation of the activity of the lysosomal enzymes
- Lubrication of the joints
- Inhibition of thrombus formation.

The PGs on the cell surface are directly or indirectly implicated in basic mechanisms such as:
- Cell division
- Cell differentiation
- Cell-cell adhesion
- Ligand-receptor recognition
- Neoplastic transformation and evolution.

▶ Each individual carries one or more genetic defects with an alteration of certain enzyme groups, not necessarily with significant phenotypic pathologies [Chromosomic or genetic alterations of matrix small proteoglycans (e.g. Progeria, Marfan syndrome); genetic alterations of splitting GAGs enzymes (e.g. Hurler syndrome, Morquio syndrome)]. These genetic defects also involve the optimal neobiosynthesis of GAGs and PGs.
During life (psycho-immune environmental stress) catabolites accumulate that progressively poison the matrix making energy exchanges difficult from and by the cells.

$$\Delta T = T_{cell} - T_{matrix} > 0$$

– The whole aging process is nothing more than the diminution of ΔT.

▶ Trincher's principle = biological time x ΔT = constant
This means that energy transformation in every cell must necessarily have a **finite time**.

## OTHER ECM CONSTITUENTS

### Glycoproteins

1) *Collagens:* 15 different types, separated into 3 groups
   – Fibrillar
   – Fibril-associated
   – Nonfibrillar.

In fibrillar collagens, the fibers are arranged in parallel, but "out of phase" longitudinally by 1/4 of their length.
All the basal membranes consist of type IV collagen.

2) *Elastin:* elastin is wound into microfibrils. Fibroblasts, macrophages, and smooth muscle cells have receptors for elastin.

3) *Reticular glycoproteins (RG):*
Fibronectin (FIG. 3), laminin, vitronectin, tenascin (hexabrachion), lectins.
The RGs bind to the integrins of the cell adhesion receptors and they influence the structure of the cytoskeleton. They participate in the constitution of the basal membranes.
The reticular glycoproteins are extremely sensitive to proteolysis.

4) *Hyaluronic acid:* is the first glycoprotein to appear in the phyletic scale (Poriphera = sponges), and it is the first one to appear in the embryo.

5) *Heparin.*

6) *Silicic acid [Si(OH)]n.*

## IMPORTANCE OF SILICIC ACID IN ECM

The regulation of the ECM, partly triggered by genetic factors, is clearly necessary for the continuous and varying exposure to physical-chemical environmental factors (TAB. 2).

An important role in matrix homeostasis is assumed by *silicic acid*.
The importance of the role of *silicic acid* [Si(OH)]n in the matrix is due to the fact

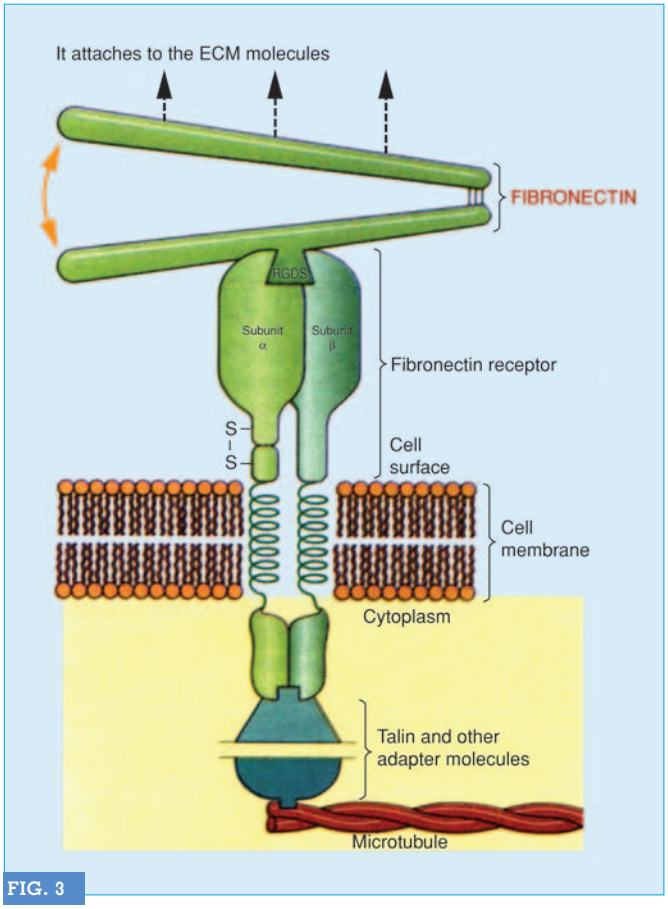



FIG. 3

**The structure and position of the fibronectin, with its classical "seesaw" behavior, modulates and synchronizes the entrance of some macromolecules into the cytoplasm from the ECM.**

that this inorganic acid can **polymerize** with great facility, as the **organic molecules** do.
Thanks to the weak bonds, it can co-polymerize with GAGs and PGs forming and strengthening the *tunnel meshes* necessary for the transport of materials in the ECM.

## IMPORTANCE OF METALLOPROTEINASES IN ECM

Matrix metalloproteinases (MMPs) or *matrixins* are high molecular weight proteins having enzymatic activity that act exclusively in the ECM. Matrixins monitor intracellular transcription and extracellular activation of cytokines.
For example: IL-1 beta has an extremely important role in cartilage turn over by means of matrixin 13 increase.
They are:
- the makers of ECM turn over
- the ECM modellers
- they act actively in Gel-Sol phases.

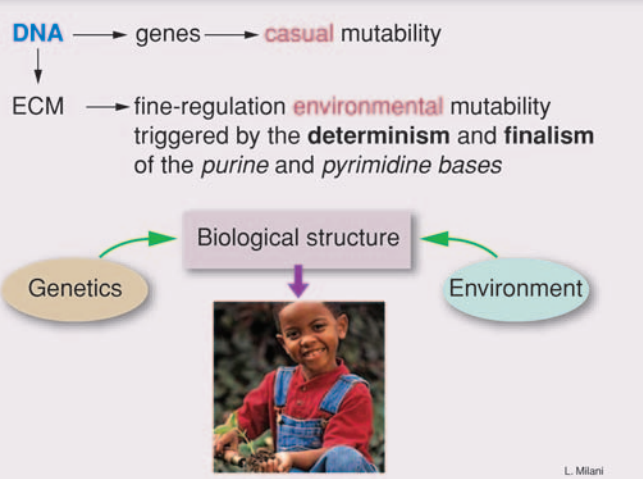
## A SANDWICH FOR LIFE

Let us consider a cell with the double phospholipid membrane (potential difference of 70 mV). The glycocalyxes are negatively charged because of the presence of sialic acid. They are connected to the cell nucleus through the microtubules, actin filaments and trabecular meshwork (FIG. 4).
The microtubules consist of 13 polypeptide chains of tubulin, made up of only 2 types (monomers) of proteins: α and ß tubulin.

Every monomer has a directed charge and the whole microtubule "forms" a dipole.
For this reason, the $H_2O$ molecules are attracted by the microtubule and assume a more orderly spatial configuration relative to the cytoplasm and the ECM.

The $H_2O$ next to the microtubule is practically immobile and disperses little energy, through which an electromagnetic signal captured by the glycocalyx and its prolongation (cytoskeleton) loses very little energy by amplifying the degree of penetration.

TAB. 2



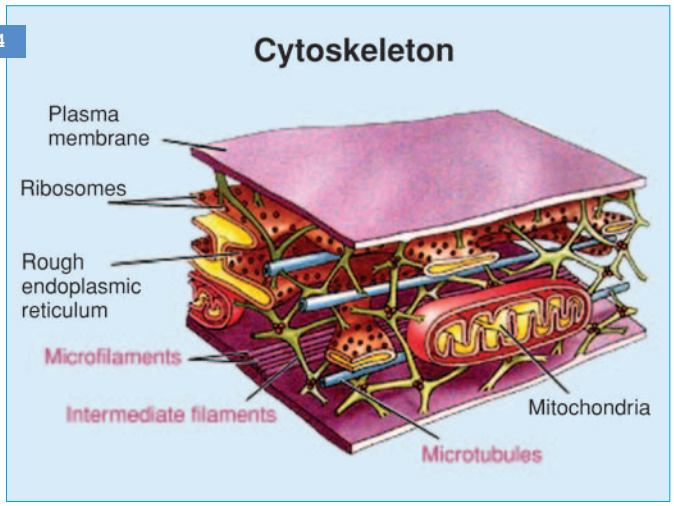

### HIGHLY CONSERVATIVE MECHANISM

Since the system passes from higher energy to lower and the electromagnetic wave frequency cannot change, the wavelength has to be reduced.

In the ECM, the electromagnetic wave is packaged to become a photon, while, passing into the cell cytoplasm, it reacquires its own undulatory structure.

- When a toxic stressor is deposited on the glycocalyx, the $H_2O$ molecules change their dielectric constant: the electromagnetic waves are not transformed into photons and are not recognized by the glycocalix → pathological event because of code non-recognition.

FIG. 4




**The microfilaments, the intermediate filaments and the microtubules do not only represent the endocellular support structures, but also the "paths" through which the exo-endocellular information passes.**

## ROLE OF THE ECM IN PHYSIOLOGICAL REGULATING MEDICINE (PRM)

ECM is the real "basic regulating system": every alteration in the external and internal environment influences cell mechanisms by means of the ECM. The communication between cells and external environment takes place through the ECM: the huge quantity of information the ECM can store are transmitted to cells as instructions for their

own physiological functioning.
In the ECM neurovegetative endings branch off; in the ECM psyco-neuro-endocrine-immunological information travels by means of neural and endocrine substances and cytokines. The information coordinates and monitors the ECM functioning through the binding with membrane receptors.
A stressors deposit at this level is the possible trigger for the onset and the development of a pathology.
- Through PRM the static notion of ECM is overcome. The connective tissue is meant as a morpho-functional unit (capillary, matrix, membrane receptor).

## GUNA®-MATRIX

Each PRM complex medicine is an optimal composition of remedies (MRP = Master Remedies Pattern), a therapeutic unit having a different and higher global effect compared to the summation of the therapeutic effects of the single ingredients; as a consequence, the former is more effective (synergy-balance-completeness principle).
In the homeo-pharmacological structure of GUNA®-MATRIX is inscribed its correct therapeutic use rationale.
In GUNA®-MATRIX composition, there are 5 different and interactive cores:

▶ **1st core**: Matrix drainage

DHEA 6X ; Prolactine 2X ; IL-6 4C ; Conjunctiva tissue, Porcine 6X ; Pyrogenium 12X ; Tyrosine 2X ; Phenilalanine 2X ; Histidine 2X.
- The therapeutic effect of the ingredients of the 1st core is:
1) increase of the ECM cynetics (protein hydrolisis, hyper-ionicity, histamine activity) and ECM turnover;
2) Symphatheticotonic stimulation;
3) Vagotonic slowdown.

▶ **2nd core**: Lymphatic drainage

Lymphatic vessel, Porcine 6X.
- The therapeutic effect of the ingredient of the 2nd core is the canalization of inactivated toxins towards the lymphatic circle for their drainage.

▶ **3rd core**: Toxins neutralization

Fucus vesiculosus 3X; Tyrosine 2X.
- The therapeutic effect of the ingredients of the 3rd core is the synergic action with Fucus of the thyroid hormones activating the sympatheticotonic nervous system.

▶ **4th core**: Action against toxin impregnation

Thuja occidentalis 6/8/12/30/200X; Natrium sulphuricum 6/8/12/30/200X; Hyaluronidase 6X; DHEA 6X; Prolactin 6X.
- The therapeutic effect of the ingredients of the 4th core is toxins centrifugation together with the potential carrying of toxins by lymphatic capillaries (see 2nd core), matrix solubilisation and general action against the dysmetabolic mesenchimopathies (in Homeopathy: sicosis).

▶ **5th core**: Metabolic support

D-L malicum ac. 6X; Lacticum ac. 3X; Ascorbic ac. 2X; Natrium oxal. 6X; Natrium pyruv. 6X; Nadidium 6X; Trichynol 6X.
- The therapeutic effect of the ingredients of the 5th core is stimulation of the energetic mitochondrial activity and ECM acidification promoting the connective reactivity.

It is possible to notice - from the analysis of the 5 therapeutic cores of GUNA®-MATRIX - that the medicine contains 20 homeopathically diluted unitary remedies:
- P.N.E.I. unitaries (DHEA 6X; Prolactin 6X; Tyrosine 2X; Interleukin-6 4C);
- Enzymes (e.g. Hyaluronidase 6X);
- Porcine derivatives (e.g. Conjunctiva tissue, Porcine 6X ; Lymphatic vessel, Porcine 6X);
- Nosodes (e.g. Pyrogenium 12X);
- Krebs cycle intermediates (e.g. DL malic acid 6X, Natrum pyruvicum 6X);
- Amino acids (e.g. Phenylalanine 2X; Histidine 2X);
- Unitaries from plant origin (e.g. Fucus vesiculosus 3X; Thuja occ. 6/8/12/30/200X).

Therefore, GUNA®-MATRIX is a complete therapeutic unit in which remedies "saturate" every phase of the etiophatogenetic cascade for the optimal deep detoxification of the ECM.

GUNA®-MATRIX is, as a consequence, indicated in the detoxification and optimal drainage of the ECM, after an acute inflammation, during and after an allopathic therapy (e.g. antibiotics, cortisone, cytostatic drugs), during and after a prolonged psychophysical stress, during the convalescence, for every chronic pathology. GUNA®-MATRIX is also a geriatric aspecific remedy particularly effective. ■

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