EXTRACTION DRUGS OF SEA ORGANISMS (INVERTEBRATES AND SMALL SEA FISH) WITH PREVALENTLY ANTIHYALURONIDASIC (PHI) ACTIVITY

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Abstract

The extraction drugs of sea organisms, invertebrates and small sea fish with prevalently antihyaluronidasic activity are anti-rheumatic, anti-inflammatory and antialgic, bring the profactors (precursors) of the aggregates from the ground substance and PHI (physiological hyaluronidase inhibitor). Their content in free amino acids, small peptides, carbohydrates (glycogen, mucopolysaccharide polymers, hexoses, pentoses etc.), micro-elements as Na, K, Ca, Mg, Fe, Cu, Zn; ensure recovery of the macromolecular structures which are disorganized in the diseases with prevalently degenerative and inflammatory components, stimulating the biosynthesis of the hyaluronic acid, of the proteoglycans and of the binding proteins, simultaneously with hyaluronidase inhibition; modulate the increased turnover of osseous calcium, inhibiting the activity of osteoclasts, diminishing the cartilage and bone degradation, through the recovery of the ground substance.

Key words: antihyaluronidase activity, extraction drugs, marine organisms

The bioactive concentrate of antihyaluronidase type from marine organisms (1), invertebrates : *Mytilus galloprovincialis*, *Mya arenaria*, *Loligo pealei* and *Euphausia superba dana* and small sea fish: *Odontogadus merlangus euxinus*, *Alosa tanaica nordmanni*, *Engraulis encrassicolus ponticus*, *Sprattus sprattus sprattus*), obtained by original biotechnology (few patents), has the composition represented in Table 1.

Table 1 : Chemical composition of an aqueous natural extract with 1% active substance,obtained from small sea fish

Active substance: 1,1g%
Antihyaluronidase activity: 100 UI/ml;
Ash: 0,070 g%;
Mineral elements: Na, K, Ca, Mg, Fe, Cu and Zn have been identified
Pb- absent, Cd-absent, Cr-absent;
Total nitrogen: 0,13 g%;
Small peptides: 0,50 g%;
Total amino acids: 0,95 g%:

- cysteine+ cystine: 0,07 g%	- alanine: 0,06 g%
- lysine: 0,02 g%	- proline: 0,06 g%
- histidine: 0,05 g%	- g aminobutyric acid: 0,23 g%
- arginine: 0,02 g%	- tyrosine: 0,01 g%
- serine: in trace	- valine: 0,04 g%
- aspartic acid: 0,06 g%	- phenylalanine: 0,18 g%
- glycocoll: 0,01 g%	- leucine: 0,08 g%
- glutamic acid: 0,06g	

Free amino acids: 0,48 g%
The same amino acids, as to the above point have been identified.
Total carbohydrates: 0,12 g%;
Glycogen: 0,10 g%;
Reducing carbohydrates (hexoses, pentoses, methyl-pentoses etc.): 0,02 g%
Acidic mucopolysaccharides: 0,01 g%

The Diffusion Test of China ink in the rat skin (Table 2), proves "in vivo" an appreciable effect of decreasing the skin permeability, due to the inhibitory action on hyaluronidase, and "in vitro" experiments prove a strong anti-hyaluronidasic activity, comparable with Merck chondroitinsulphates solution (Table 3). The anti-inflammatory and tissue-restitutive effect consists, on the one hand, in inhibition of the hyaluronidase that becomes unable to depolymerize the hyaluronic acid and, on the other hand, under the action of hyaluronidase as a starter of the enzyme-substrate relation, in stimulation of hyaluronic acid biosynthesis process. Thus, in the presence of the enzyme and plenty of specific chemical compounds (Table 1), "in vivo" biosynthesis of hyaluronic acid occurs from theirs components (2). Also, the two phenomena, on the one hand enzyme inhibition resulting in neutralization of hyaluronic acid depolymerisation and, on the other hand, under the action of the same enzyme, the hyaluronic acid synthesis from its components in a "environment" consisting of a set of specific chemical compounds, including cations with a very important contribution lead synergically to a joint final result, that is the anti-inflammatory and tissue-restitutive effect, also initiating other enzymatic restructuring processes like the cartilage structures. From the above data, it results that the anti-hyaluronidasic activity and tissue-restitutive effect is given by the ensemble of specific chemical compounds. Thus, the anti-inflammatory effect of the Romanian drugs called *ALFLUTOP*^{R} and *ARMADENT*^{R} consists in the inhibition of the hyaluronidase and probably in the activation of the superoxide dismutase, inhibiting the process of breakdown of the hyaluronic acid and chondroitinsulphates (3). In conclusions, taking into account that the cell proliferation and inflammation depend on the destruction of the ground substance by the cellular hyaluronidase, there are two pathways of therapy control in which the excessive cell proliferation is a harmful feature:

1. The increase of the ground substance resistance against the enzymatic destruction or the regeneration of the ground substance due to the administration of ancestors (precursors), necessary for the biogenesis of the acidic mucopolysaccharides (hyaluronic acid and chondroitinsulphates).
2. The direct neutralisation of the cellular hyaluronidase due to the decrease of the production by the cells or to the inhibition of its enzymatic action which offer more rapid therapy possibilities.

Table2 : "In vivo" specific antihyaluronidasic activity

	Blank	Hyaluronidase (H)	H+P1	H+P2	H+P3	H+P4	H+P5
Content in 0,1 ml aqueous solution		7,54	7,54+10mg	7,54+10mg	7,54+10mg	7,54+10mg	7,54+10mg
Average value of diffusion surface in mmp	107,3 78,6 91,9	175,9 199,8 174,9	58,5	16,5	43,2	25,8	11,9
Permeabilising effect (percentage - %)		+64 +154 + 90					
Antihyaluronidasic effect (percentage - %)			-67 6,9 p.0,001	-91 11,1 p.0,001	-79 6,1 p.0,001	-87 7,1 p.0,001	-94 5,0 p.0,001
Skin permeability decreasing effect			171%	232%	129%	143%	196%

Table 3 : Antihyaluronidasic activity of the bioactive preparation obtained from different species of marine organism in comparison with data in the speciality literature

Preparation	Antihyaluronidasic activity	Literature
Sodium Chondroitine Sulphate (Merck)-0,1% solution	50 IU/ml = 5,0 IU/mg	ROSOIU, 1982
Antihyaluronidase from *Loligo pealei*	79 IU /ml = 7,9 IU/mg	ROSOIU, 1982
Antihyaluronidase from *Euphausia superba dana*	84 IU /ml = 8,4 IU/mg	ROSOIU, 1982
Antihyaluronidase from *Alosa tanaica nordmanni*	73 IU /ml = 7,3 IU/mg	
Antihyaluronidase from *Odontogadus merlangus euxinus*	83 IU /ml = 8,3 IU/mg	ROSOIU, 1982
Antihyaluronidase from Engraulis encrassicholus ponticus	93 IU /ml = 9,3 IU/mg	ROSOIU, 1982
Sulphomucopolysaccharides from *Mytilus galloprovincialis*	3,2 IU /mg	MOLNAR *et al.*, 1976
Sulphomucopolysaccharides from *Mya arenaria*	5,0 IU /mg	MOLNAR *et al.*, 1976
Sulphomucopolysaccharides from fowl small intestine	4,8 IU /mg	MOLNAR *et al.*, 1976
Sulphomucopolysaccharides from cattle duodenum	5,0 IU /mg	MOLNAR *et al.*, 1976

The cellular proliferation process is controlled by the presence in the tissues and in blood of a substance called physiological hyaluronidase inhibitor (PHI). The serum PHI (antihyaluronidase) exists in a normal, well determined concentration in health state. The orthomolecular medicine approaches both health preservation and treatment of diseases through the quantitative variation in the human body of certain substances that are also normally present in it.Thus, the biologically active extraction concentrate of sea organisms with prevalently antihyaluronidasic activity, obtained by us, bring the ancestors (precursors) of the aggregates of the ground substance and PHI (physiological hyaluronidase inhibitor). Thus, free amino acids, small peptides, carbohydrates (glycogen, mucopolysaccharides, hexoses, pentoses etc,), microelements as Na, K, Ca, Mg, Fe, Cu, Zn; ensures recovery of the macromolecular structures which are disorganised in the diseases with prevalently degenerative and inflammatory components, stimulating the biosynthesis of the hyaluronic acid, of the proteoglycans and of the binding proteins, simultaneously with hyaluronidase inhibition; modulates the increased turnover of osseous calcium, inhibiting the activity of osteoclasts, diminishing the cartilage and bone degradation, through the recovery of the ground substances, the fine balance between synthetic and degrade processes which are of significance in both health and disease.

References

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