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INFLAMMATION - NEW TRENDS IN ASSESSMENT AND CONTROL AT THE PHYSIOLOGICAL LEVEL

SUMMARY

Pain is a complex process and can be classified into four categories namely:
1) Physiological pain, related to the preservation of life, associated with a short-term inflammation level.
2) Nociceptive pain, related to the long-lasting inflammation; it is usually chronic.
3) Neuropathic pain, usually chronic, results from damage, compression or dysfunction of the peripheral nerves or neural *loops* in the CNS.
Inflammation is usually associated with pain, but it can be pain without inflammation, such as the neuropathic pain.
4) Mixed pain in which various factors are involved. The best example is the pain associated with cancer, which is chronic, permanent and difficult to control for which the use of analgesics is frequently combined with opioids.
Interleukins are the primary means of intercellular communication against an aggression starting the inflammatory response.
Physiological Regulating Medicine has really filled a gap and allowed to settle two main problems controlling the inflammation and pain, despite the existence of NSAIDs for more than a century, with a biological approach, respecting the physiological processes without the risk of unwanted strong side effects associated with the conventional medicines already known.
The 11 products are: Guna®-Neck, Guna®-Thoracic, Guna®-Lumbar, Guna®-Shoulder (shoulder and elbow), Guna®-Hip, Guna®-Knee, Guna®-HandFoot, Guna®-Ischial, Guna®-Polyarthritis, Guna®-Muscle, and Guna®-Neural, of which 10 contain β-endorphin 4C [equivalent to nanograms (ng)].
Nine products of these contain Anti IL-1 α and β 4 C [equivalent to nanograms (ng)], which ascribe an analgesic and anti-inflammatory effect at the physiological level without the side effects of medications known.
Excellent results are obteined for: bursitis, epicondylitis, fibromyalgia, osteoarthritis of the hip and knee, sacroiliitis, cervical pain, thoracic pain, low back pain, trigeminal neuralgia, etc.

KEY WORDS **PHYSIOLOGICAL REGULATING MEDICINE, PAIN, INFLAMMATION, NERVE IRRITATION, CYCLOOXYGENASES, INTERLEUKINS, B-ENDORPHIN, INJECTABLE AMPOULES**

INTRODUCTION

The word inflammation derives from Latin "*inflammare*" (to light a fire).

It is a process where the body fights against an "irritant agent" at the level of receptors (nociceptors), and it essentially characterized by: pain, swelling, heat, redness, and loss of functions.

Nociceptors are sensitive receptors to damage; they act as transducers and conduct nerve impulses to the Central Nervous System (CNS) through small **A- delta fibers** (myelinated, fast) for acute pain, and **c fibers** (slow, unmyelinated) for chronic pain.

When a tissue is damaged, its cells release various substances that cause blood vessels dilatation, and therefore greater blood supply to the triggered area.

Furthermore, in the affected tissues, the inflammatory exudate **increases** capillary permeability, leukocyte migration, the presence of cytokines and other local processes that excite and "irritate" the nerve endings, making the physiological functioning of the area blocked.

– All this, within the so-called **arachidonic acid *cascade***.
The inflammatory response occurs with a defending goal in order to isolate and destroy the damaging agent, as well as repairing the tissue of the damaged tissue/organ; when the inflammation is chronic it occurs a local tissue destruction, and therefore it is difficult to restore the lost functions.
Inflammation can be short term in association with physiological pain, but when kept beyond expectations should be considered chronic, and it is the result of a **longer neuron irritation at the receptors level**, with periods of greater or less intensity.
– In this situation, it is higly recommended an effective treatment, avoiding side effects.

– This paper discusses the importance of clinical control of inflammation with specific *low dose* formulations (S.K.A.) and for different anatomical areas, formulated with the intention to restore optimal physiological states avoiding undesirable side effects, according to the Principles of the Physiological Regulating Medicine (PRM).

PAIN

We have previously pointed out that pain is a complex process; it can be classified into four categories, namely:

1) **Physiological pain**, related to the preservation of life, associated with a short-term inflammation level.

2) **Nociceptive pain**, related to the long-lasting inflammation; it is usually chronic.

3) **Neuropathic pain**, usually chronic, resulting from damage, compression or dysfunction of the peripheral nerves or neuronal *loops* in the CNS.
Inflammation is usually associated with pain, but can be pain without inflammation, such as the **neuropathic pain**.

4) **Mixed pain** in which various factors are involved.
The best example is the pain associated with cancer, which is chronic, permanent and difficult to control for which the use of analgesics is frequently combined with opioids (1-7).

In this work we will discuss matters related to inflammation.

CYTOKINES IN INFLAMMATION

Cytokines are polypeptides mainly produced by activated lymphocytes and macrophages, but can also be produced by elements of the connective tissue.
According to the cells that produce them, they take their name: **lymphokines**, **monokines**, **interleukins**.
Interleukins are cytokines; the name comes from Greek language *leukós* (white) and *kinè* (movement).
– Interleukins act as *chemical messengers* within short distance.
Their main functions is to regulate the events concerning within the Immune System functions and the mechanism of inflammation.
Interleukins are the primary means of intercellular communication against an aggression, starting the inflammatory response.

There are **pro**-inflammatory cytokines and **anti-**inflammatory cytokines.
At least 33 interleukins are now known.

– **Th1** lymphocytes produce pro-inflammatory interleukins **IL-1α**, **IL-1β**, **IL-2**, **IL-6**, etc.

– **Th2** lymphocytes produce anti-inflammatory interleukins **IL-4**, **IL-10**, etc.
The complex process of inflammation is regulated partly by the balance between Th1/Th2 lymphocytes (8-11).

Inflammation is a physiological process in response to tissue aggression.
The injury causes the release of phospholipids (PL) of the cellular membrane; PL are transformed by the action of the enzyme phospholipase A2 into arachidonic acid (**AA**).

The AA, in the presence of the enzymes cyclooxygenases (**COXs**), produces prostaglandins (**PGs**).
The PGs excite the nerve endings (nociceptors) triggering the sensation of pain and starting the inflammatory process where at the site of injury other mediators are released, such as **bradykinin**, **histamine**, **nitric oxide**, **interleukins**, etc.

– So far it has been demostrated different ways starting from the transformation of the AA:

1 - The way of the **5-lipoxygenase** to the leukotrienes (LT), which are extremely smooth muscle constrictors and participate in the processes of the chronic inflammation, increasing vascular permeability and favoring the edema of the, affected area.
– *Low dose* aspirin is a specific inhibitor of this pathway, while avoiding the action of thromboxanes.

2 - The way of **COX-1** (present in the tissues) to PGs E2, with the result of stimulating pain receptors.
Must be noted that there exists cytoprotective PGs mainly preserving the stomach and kidney functions.
– Here the NSAIDs, are inhibitors of this way at pharmacological doses, but do not inhibit the lipoxygenase pathway and therefore **do not** eliminate, the formation of leukotrienes.

3- The way of **COX-2** to PGs (does not exist in physiological conditions), mainly related to inflammation.
– Here the conventional NSAIDs are inhibitors of this pathway when using high doses or if we use the selective COX-2 inhibitors such as **nimesulide**, **celecoxib** at pharmachological doses, which are low compared to other NSAIDs (12,13).

4 - The way of **COX-3** (present only in the brain and in the heart) involved with PGs related with fever.
– Here **paracetamol** has shown specific inhibition of this pathway (14,15) (FIG. 1).

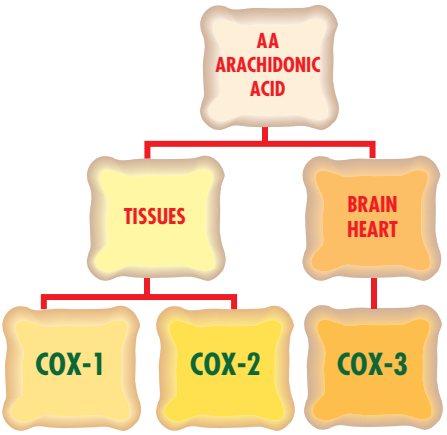

FIG. 1

5 - There is the inhibition of PGs starting from blocking the phospholipase.
– Here **steroids** have shown therapeutic effectiveness.

6 - Interleukins besides activating COX 2, stimulate nitric oxide (NO) synthase enzyme (FIG. 2), increasing the NO levels starting from the L-arginine acting as a free radical, as a pro-inflammatory element of short-term and local action.

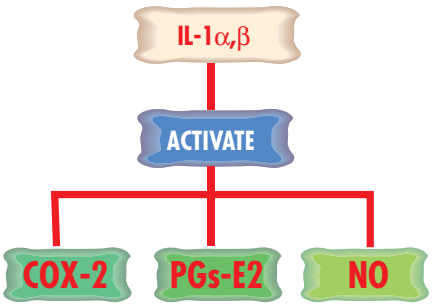

FIG. 2

– Here **salicylates** reduce the NO levels.

In all these cases we cannot fail to mention the side effects of the conventional medicines listed above.

We note the following: **IL-1α**, **IL-1β** are the main factors triggering the inflammation by activating **COX-2**, **PGsE2**, and **NO**, which are responsable for provoking irritation of nociceptors.

– An anti-inflammatory effect from the physiological point of view is induced by the use of **Anti-**interleukins with other elements that sinergically achieve excellent results in the control of inflammation (FIG. 3).

On the other hand, a decrease in **β-endorphin** is one of the factors that maintain neuropathic pain for a prolonged period in a chronic form.

Finally we can define that when there is a neuronal irritation at the nociceptor level, the clinical expression is Inflammation. Pro inflammatory interleukins here are the most important factors in their evolution, instead of a neuronal irritation in CNS; the disturbance is at the synaptic level, and is modulated largerly by the **levels of glutamate**, excitatory neurotransmitter, and by β-endorphin with high analgesic power where the latter plays an important role in its control.

In this case the clinical manifestation is pain (neuropathic).

– Lastly irritation at the cortical level results clinically as convulsions.

The clinical expression is different, depending on the location in the CNS where the neural irritation occurs (FIG. 4).

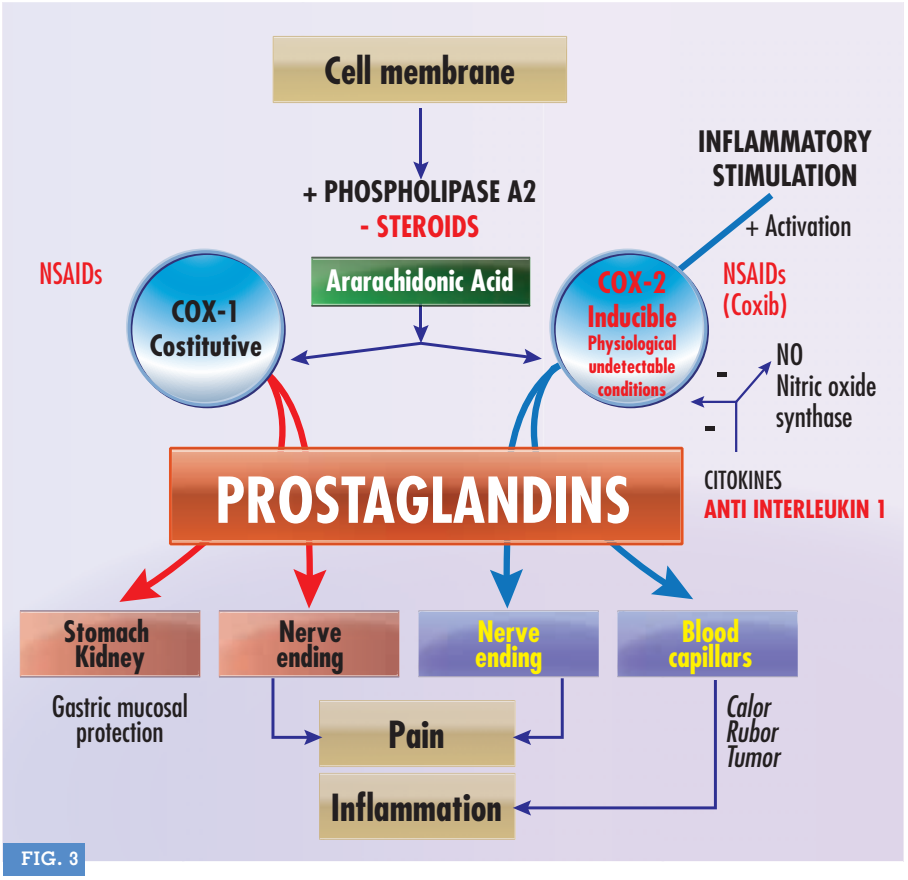

FIG. 3

USE OF *LOW DOSES* FROM THE ORIGINAL SUBSTANCE

One of the Principles of Physiological Regulating Medicine (PRM) is to provide *low-dose* formulations, intended to avoid the unwanted side effects usually produced by the conventional drugs.

Low dose medicine (PRM) are created mainly with substances from plant, animal and/or mineral origin and can be prepared in two main dilutions: **Decimal (X)** and **Centesimal (C)**.

The first, when a part of the Mother Tincture (TM) is diluted in 9 parts (total 10 parts); on the other hand in the second one when a part of the Mother Tincture is diluted in 99 parts (total 100 parts), repeating the procedure until the desired dilution is obtained, 1X, 2X…or 1C, 2C, 3C, 4C…..and are classified as: **Low Dilution**, between **2X – 8X** (10^{-2}-10^{-8}) or 1C

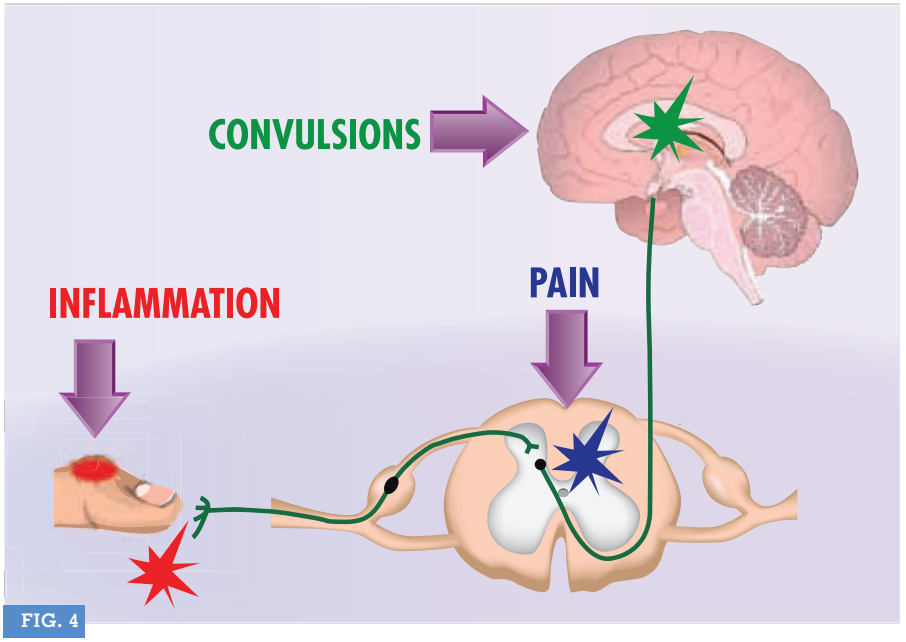

FIG. 4

– 4C, **Intermediate Dilution** between 9X – 23X (10^{-9}-10^{-23}) or 5C -11C, and **High Dilution** above 24X or 12C (>10^{-24}).
In the first two dilutions (low and intermediate) active molecules are present, on the contrary in the high dilution there are no active molecules, for exceeding the Number of Avogadro.
– Ultimately to be therapeutically effective dilutions must be complemented with a dynamic process (**SKA** = Sequential Kinetic Activation), consisting in vigorous shaking and giving special characteristic to these formulations (16,17).

As regards PGsE2, thromboxanes and leukotrienes are considered as an "*hormonal*" *group* more, as such they act locally, but sometimes act on distant tissues, all of them are involved in many physiological processes, such as the inflammation at concentrations corresponding between 10^{-9} – 10^{-12} g (9X-12X or C4-C6) respectively, which are the dilutions most used in Physiological Regulating Medicine formulations.

Other studies have shown that *low doses* interact at the cell nucleus level, while the effect of high concentrations is mostly at the cytoplasmatic level (18).

CONCLUSION AND RECOMMENDATIONS

Physiological Regulating Medicine has really filled a gap and allowed to settle two main problems controlling the inflammation and pain, despite the existence of NSAIDs for more than a century, with a biological approach, respecting the physiological processes without the risk of unwanted strong side effects associated with the conventional medicines.

It is well known that the release of mediators direct of hyperalgesia is secondary to the release of interleukins in the process of inflammation, particularly IL-1α, IL-1β, responsible for the nociceptors "irritation" through PGs.

Likewise, bradykinin may contribute to further release of cytokines (interleukins) apparently mediated by TNFα. NSAIDs have the intention either of blocking the enzyme cyclooxygenase (COX-1) or selectively (COX 2), such as celecoxib; on the other hand nimesulide inhibits the release of TNFα.
In all cases the anti-inflammatory effect is achieved by reduction of PGs (12, 13).

Corticosteroids reduce PGs by stimulation of lipocortin. Lipocortin blocks the activity of phospholipase A2 inhibiting the release of PGs by decreasing of the enzyme cyclooxygenase.

On the other hand, salycilates decrease levels of cytokines by inhibiting the enzyme NO synthase, with which lowers the levels of NO starting from L-arginine.

Additionally, the proposed drugs for neuropathic pain have tendencially been tipped for the use of antiepilectic drugs, antidepressant and others with the intention of relieving pain by acting on the CNS at the synaptic level, especially associated with diabetic neuropathy and fibromyalgia (19, 20). This type of pain is modulated largely by the levels of neurotransmitters glutamate (excitatory) and β-endorphin (inhibitory), which own a high analgesic power.

As noted above, we can achieve an anti-inflammatory effect starting from the utilization of **Anti-Interleukins pro-inflammatory** (Anti-IL-1 and y β), in physiological doses, with the intention of decreasing COX-2 levels without the adverse effects of NSAIDs.

With this background we can better understand the objectives of Physiological Regulating Medicine, with 11 injectable ampoules and others oral, to control inflammation and pain.
The formulations contain also: **Anti-interleukin 1** (Anti IL-1 α and β) and **β-endorphin**, with the intention to act at the physiological level and in the complex process of inflammation and pain.

The 11 PRM injectable products are: **Guna®-Neck**, **Guna®-Thoracic**, **Guna®-Lumbar**, **Guna®-Shoulder** (Shoulder and elbow), **Guna®-Hip, Guna®-Knee**, **Guna®-HandFoot**, **Guna®-Ischial**, **Guna®-Polyarthritis**, **Guna®-Muscle**, and **Guna®-Neural**, of which 10 contain β-endorphin 4C [equivalent to nanograms (ng)]. Nine products of these contain Anti IL-1 α and β 4 C [equivalent to nanograms (ng)], which ascribe an analgesic and anti-inflammatory effect at the physiological level without the side effects of medications known (FIG. 5) (21).

THE 11 PRM INJECTABLE *LOW DOSE* PRODUCTS FOR THE PAIN CONTROL

10 out of 11 contain β endorphin

9 out of 11 contain Anti-IL 1α, and Anti-IL 1β

FIG. 5

Excellent results are obtained in: bursitis, epicondylitis, fibromyalgia, osteoarthritis of the hip and knee, sacroiliitis, cervical pain, thoracic pain, low back pain, trigeminal neuralgia, etc. (22,23,24).

The powerful anti-inflammatory effect of these products is namely due to several factors.
The Anti Il-1α and β *low dose* inhibit COX-2, PGs and nitric oxide (NO), obtaining the same result of NSAIDs, steroids and salicylate, respectively, without contraindications or side effects (8).

For over a century medicine doctors have fought for the noble task of relieving pain; in this work doctors set out the worthy results of a Group of scientists and researchers who have come together in Italy and brouhgt new ideas in the control of pain and inflammation, resulting in an innovative concept (Physiological Regulating Medicine), with the same objective to contribute in the hope of every person to be free of pain without unwanted side effects.

– We hope, this is an encouraging start for the medical community to have a new method in the relentless battle against the evil that is inflammation and pain. ■

Bibliography

1. Urgelles, L.A.: Dolor nociceptivo vs. neuropático: Medicina Fisiológica de Regulación (FMR) Nuevo enfoque para su control. Rev. Mexicana de Algología. **2008**: 5: 10 :17-22.
2. Urgelles, L.A.: Nociceptive Pain vs. Neuropathic Pain - A new classification for Pain Control. Physiological Regulating Medicine, Italy. **2008**: 1; 39-42.
3. Urgelles, L.A.: La clínica del dolor en oncología: un objetivo inmediato. Rev. Cub. Oncol. **1989**: 5; 1-2: 51-64.
4. Urgelles. L.A.: Dolor y Cáncer. Rev. Selecta Médica. Colombia, **1998**: 9: 3: 25-26.
5. Ventafridda, V, et al.: A validation study of the WHO method for cancer pain relief. Cancer **1987**: 59 ;851-856.
6. Ventafridda, V.: Continuing care: a major issue in cancer pain management. Pain. 1989: 36:137-143.
7. Russell, K.P.: Three-step analgesic for management of cancer pain. Medicine News. **2007**: 5: 6: 81-91.
8. Milani, L.: Inflammation and Physiological Regulating Medicine: New ideas and innovative medical products. PRM, 1. **2007**; 19-27.
9. Lester, A.D.: Chemokines-chemotactic molecules that mediate inflamation. Journal of Medicine. New England.**1998**: 338: 436-445. (*in* 8-Milani, L.)
10. Bianchi, I.: Th1/Th2 balance diluted and potentized cytokines; the role of physiological regulating medicine in immunoregulation. Loyola University. Chicago. USA. Nov. **2007**.
11. Brynskov, J. et al.: Increased concentrations of interleukin-1 beta, interleukin-2 and soluble interlaukin-2 receptor in endoscopical mucosal biopsy specimens with active inflamatory bowel disease. Gut. **1992**: 33:1:55-58.
12. Urgelles, L.A.: Nimesulida: nuevo AINE en el alivio del dolor asociado al cáncer /Nimesulide: a new NSAIDs asociate in the mitigation of cancer pain. Clín. Méd. H.C.C. Venezuela. **1996**. 1:2 :78-82.
13. Urgelles, L.A, and L.F. Cifuentes: Celebrex (celecoxib). Analgésico del milenio. J. Clínica en Odontología. Venezulea. **2002**; 17(2)105-109.
14. Chandrasekharan, N.V. et. al.: COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc. Natl. Acad. Sci. USA. **2002**: 99 (21):13926-31.
15. Botting, R.: COX-1 and COX-3 inhibitors.Thrombosis Research.2003:110:5-6: 269-272.
16. Linde, L. et. al.: Are the clinical effects of homeopathy placebo effect?. a meta-analysis of placebo controlled trials. Lancet. **1997**: 350:834-843. (*in* 17-Ricottini, L)
17. Ricottini, L.: From homeopathy to physiological regulating medicine: highlights. Physiological Regulating Medicine, Italy. **2008**: 1; 31-35.
18. Stumpf, W.E.: J. Pharmacol. Toxicol. Methods. 2005; 51:1;25. (*in* 8-Milani, L.).
19. Kuritzky, L. and G. Samraj: Current treatments in the management of diabetic peripheral neuropathic pain. Pain Medicine News. **2007**: 5 :6:11-20.
20. Gupta, K.: Prevalence, diagnosis and management of fibromyalgia. Medicine News **2007**: 5: 6:32-36.
21. Milani, L.: Pain Management. Guna Injectable Ampoules. Guna S.p.a., Italy, **2007**. www.gunainc.com
22. Urgelles, L.A.: Medicina Fisiológica de Regulación en el manejo del Dolor. 3er. Tour Mexico. **2008**.
23. Milani, L.: Homeomesotherapy for pain management in primary chronic coxarthrosis with a homeopathic injectable formulation. Physiological Regulating Medicine.**2006**: 1: 9-18.
24. Milani, L.: Innovative treatment concepts in Traumatology, Fibromyalgia, Pain and Sport Medicine with PRM. Syllabus. 3rd USA National Tour. November **2007**.

Suggested readings:
www. gunainc.com → Pysiological Regulating Medicine for the following articles:

1. Milani, L.: Homeomesotherapy for pain management in primary chronic coxarthrosis with a homeopatic injectable formulation. Physiological Regulating Medicine. **2006**: 1; 9-18.
2. Milani, L.: Inflammation and Physiological Regulating Medicine- New ideas and innovative medical products. Physiological Regulating Medicine. **2007**: 1; 19-27.
3. Milani, L.: PRM homeomesotherapy and myofascial triggers: a victorious combination. Diagnosis, clinic, therapy. Physiological Regulating Medicine. **2008**: 1; 19-27.
4. Hermann G.F. *et* Al: Pain management in cervical chronic myofascial trigger points: PRM homeomesotherapy vs. conventional mesotherapy - Results of a cohort, controlled clinical trial. Physiological Regulating Medicine. **2008**: 1; 3-10.
5. Ruocco A. *et* Al: PRM mesotherapy vs conventional mesotherapy in chronic lumbago and lumbosciatica - related pain control. Results of two cohort, controlled clinical trials. Physiological Regulating Medicine. **2009**: 1; 23-30.

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