

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Nonsteroidal Anti-inflammatory Drugs: Integrated Approach to Physical Medicine and Rehabilitation

Rosa Grazia Bellomo, Simona Maria Carmignano,
Tommaso Palermo, Lucia Cosenza,
Andrea Saggini and Raoul Saggini

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.69257>

Abstract

Inflammation is an immediate response to damage; in acute phase, it is a form of defense for body and it aims to *restitutio ad integrum*, in the chronic form itself becomes disease. This mechanism determines inflammatory diseases that are a group of clinical disorders which are characterized by abnormal inflammatory responses such as osteoarthritis, in myalgic syndromes (like fibromyalgia or miofascial syndrome), in some forms of headache, in peripheral vascular disease, in many malignancies. In Physical and Rehabilitation Medicine, the use of analgesic drugs (including NSAIDs) is a crucial resource inside a complex bioprogressive rehabilitative project. A part of the classic use *per os* is characterized by a serious and systemic side effect and there is also a possibility to administer drugs through other routes. Antalgic and rehabilitative mesotherapy (ARM) is a minimally invasive technique consisting of subcutaneous injections of bioactive substances. Other alternatives are represented by iontophoresis, phonophoresis, phytotherapy, and topical application. The purpose of this chapter is to give an overview about the state of the art regarding the use of NSAIDs in physical medicine and rehabilitation.

Keywords: NSAIDs, antalgic and rehabilitative mesotherapy, iontophoresis, phonophoresis, phytotherapy

1. Inflammation

Inflammation is an immediate response to damage to tissues and cells by pathogens, noxious stimuli such as chemicals, or physical injury. Already in the short-term, there is an attempt at healing with white blood cells that arrive in the damaged area for repair process. Chronic inflammation, indeed, is a prolonged response that involves active inflammation, tissue destruction, and delays repair. Chronic and persistent inflammation is associated with many chronic human conditions and diseases, including allergy, atherosclerosis, cancer, arthritis, and autoimmune diseases. Acute inflammation is characterized by abrupt onset, followed by a rapid succession of events (hours or days) essentially vascular (hence angiophlogosis) responsible for the cardinal signs, culminating in the resolution or chronicity. Chronic inflammation has greater duration of the previous form (months or years), with oscillations of the gravity and phenomena of intensification during its evolution. It is also defined as istophlogosis, for the prevalence of tissue phenomena due to infiltration of mononuclear blood cells [1]. The cardinal symptoms of inflammation, described by the Roman physician Aulus Cornelius Celsus (30 before Christ - 38 Anno Domini), are: calor, rubor, tumor, dolor, who later Galen (130–200 AD) added *functio laesa*, indicating the functional impairment.

Inflammation process is a reaction triggered by innate immunity mechanisms, which evolved in a pattern that can vary based on etiologic agent, the headquarters of the damage and the intensity of the damage.

The mechanism underlying inflammation process is connected to the physiological state of homeostasis. Several studies suggest that inflammation operates as a much-sophisticated system than ever thought at the molecular level. The inflammation is mainly a local reaction, which generates a systemic response when it exceeds a certain threshold and molecules, synthesized and released into bloodstream in response to the damage, acting on distant organs that express receptors for them. As longer this response persists in the host will encounter the more damaging consequences [2]. Increased vascular permeability, that is a feature of acute inflammation, leading to the leakage of a protein-rich fluid (exudate) in the interstitium, to this, follows a variation of interstitial pressure (increases) and intravascular pressure (decreases). The presence of exudate and the hydrostatic pressure difference, draws fluid in the interstitial tissue with net result of edema. The first cellular step is represented by inflammatory stimuli that are first recognized by the host cells through specific transmembrane receptors, called pattern recognition receptors (PRRs), which are expressed by cells of both innate and adaptive immune systems. PRRs are responsible for sensing the presence of infecting microorganisms as well as the incidence of any cellular injuries. Disintegration of the tissue cells affected (with relative release of intracellular substances) determines the mobilization, through the blood, of the immune cells that reach the site of the lesion to begin a defence and repair process (activities mediated by substances released by these same cells) [3].

Once activated the inflammatory response, we see the release of chemical mediators that quickly induce alterations in the microcirculation, i.e., the vessels interposed between the

small arteries and small veins, arterioles, capillaries and venules. Thus, it began the vascular phase of inflammation, characterized by vasodilation and increased permeability.

The cells of the host's immunocompetent system also (among which should be mentioned macrophages, polymorphonuclear granulocytes, the mast cells, fibroblasts and platelets) contribute to the process. Subsequently, mediators such as bradycin, histamine, serotonin (5-HT, 5-HydroxyTryptamine), prostaglandins (prostaglandins (PGs), cytokines (including Interleukin (IL) and tumor necrosis factor (TNF) and some nerve growth factors Fabric, including nerve growth factor (NGF), neurotrophic factor derived from glial cell line (GDNF) and the neurotrophic factor derived from the brain (BDNF), are released [4]. Furthermore, it must consider the role of cyclooxygenase 2 (Cox-2, cycle-oxygenase-2), enzymes that, by acting inside of fibroblasts, favour the production of PGs, which have a great importance in causing inflammation and the ache. To complete the process of the liberated substances and widespread during the inflammatory process, among these must be counted calcitonin gene-related peptide (CGRP), which activates the nociceptors, and Nitric oxide (NO), gas with great ability to spread among tissues and responsible for the neurotoxic effects. A neurochemical response from the same nerve cells is involved in pain perception (neurogenic inflammation). The damaged cells release a large amount of chemicals, including, in particular, some ions (mainly hydrogen ions, H⁺, responsible for local acidosis) and adenosine triphosphate (ATP) [5, 6]. (Figure 1)

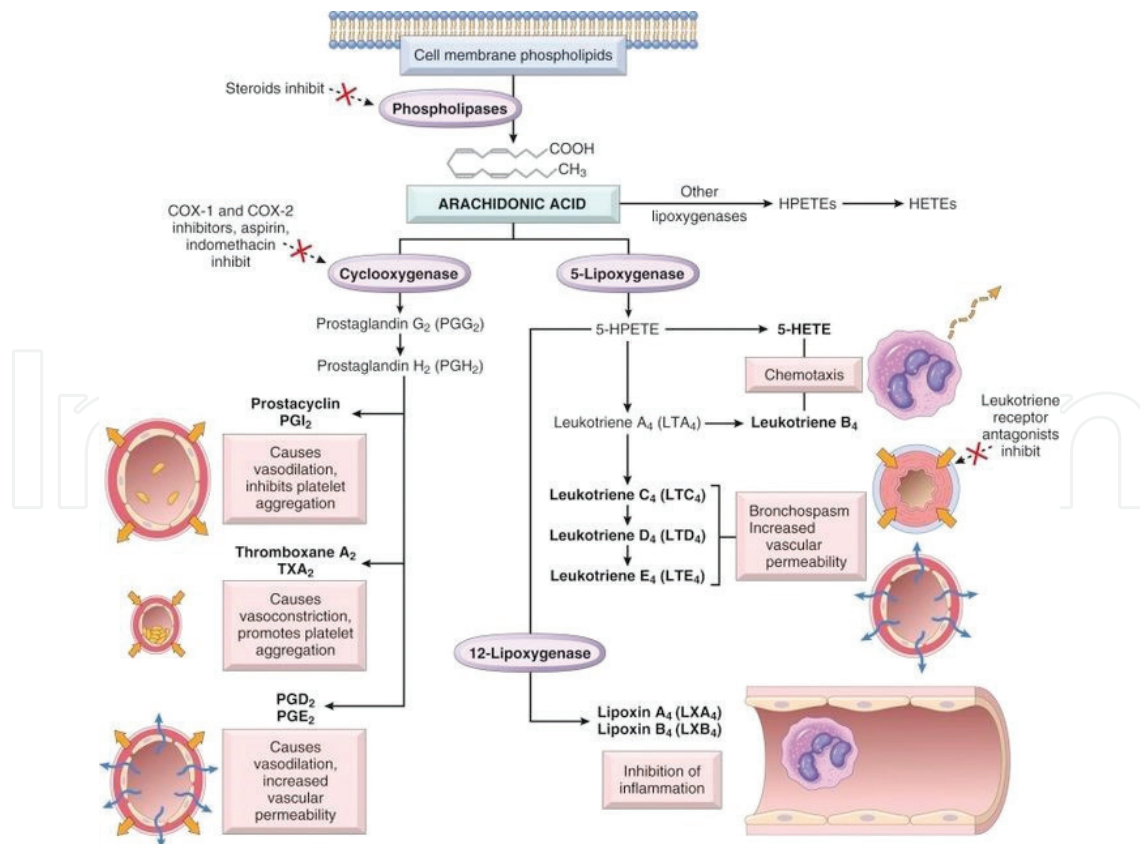


Figure 1. Inflammatory process.

All these substances have an active role in the onset of pain, a phenomenon closely related to inflammation [7]. Since the sensory nerve endings possess a variety of receptors designed to bind with the inflammatory mediators, some of the freed molecules such as adenosine triphosphate and hydrogen ions, act on nociceptors, activating them directly and causing an immediate depolarization, starting a painful stimulus. Other substances, instead, act on other receptors that are not able to start the painful stimulus but which are capable of sensitizing nociceptors, or to lower the activation threshold. While the first category of brokers, the depolarizing substances, causes pain, the second category, that of sensitizing substances, causes hyperalgesia. Among the substances that sensitize the receptors necessary to signal, there is the serotonin (5-HT), which is commonly released from platelets and mast cells in damaged tissue and inflamed. It acts by activating two receptor subtypes (5-HT₂ and 5-HT₃ receptor), whose action is synergistic with that of the receptors for bradykinin and for PGs. An inflammatory process of a somatic structure is manifested in particular with pain of varying intensity in relation to the release of active chemical mediators on algo-sensitive endings. Spinal reflexes of defence, through an increase in skeletal muscle tension, and hyperactivity of the sympathetic, contribute to the alteration of the microenvironment and the maintenance of the effects on nociceptors. The ultimate step in the elimination of traumatic agents and necrotic cells is their degradation within neutrophils and macrophages, which occur most efficiently after activation of the phagocytes. An efficacy system of host defence minimizes the damage and finally it controls the end of process. In fact, inflammation declines simply because the mediators of inflammation have short half-lives, but also because stop signals are released, they block the process [8].

In this way, in fact, the switch of arachidonic acid's metabolism acts toward the production of anti-inflammatory lipoxins, the release of transforming growth factor- β (TGF- β), an anti-inflammatory cytokine, from macrophages and other cells; and the cholinergic discharge that inhibit the production of TNF in macrophages [9].

The acute inflammation turns into a chronic one, when the process of resolution fails. Pathological states characterized by chronic inflammation are still under investigation, because in the West there are a great number of patients with these conditions, and also because the mechanisms that underlie chronic inflammation are not yet well understood. Chronic diseases, often, are not triggered by infections or pathogens and this make the understanding of their pathological processes much more complicated [10]. Chronic phlogosis is the cause of these conditions and it is not derived by xenobiotics, but it is generated by inflammatory cells that act against the host itself. This mechanism determines inflammatory diseases that are a group of clinical disorders which are characterized by abnormal inflammatory responses such as osteoarthritis, in myalgic syndromes (like fibromyalgia), in some forms of headache, in peripheral vascular disease, and in many malignancies [11].

2. From pathophysiology to pharmacology

The study of inflammatory pathophysiology was crucial stimulus to the search for substances pharmaceutically active on related symptoms. NSAIDs are mainly anti-inflammatory, but

also analgesic and antipyretic drugs. They are typically used in the treatment of pain, to reduce stiffness, and to enhance function in patients with musculoskeletal disorders, osteoarthritis, rheumatoid arthritis, and other forms of arthritis. Furthermore, NSAIDs are also used for the treatment of acute pain including headache, dysmenorrhea, and postoperative pain [12, 13].

Acetylsalicylic acid (ASA), better known as aspirin, is the prototypical NSAID. ASA traces its origins back to willow bark, a natural source of the chemical salicylate. All NSAIDs interrupt the production of inflammatory and pain-related hormones called prostaglandins. The isolation of salicylic acid in the nineteenth century from willow and poplar barks led to its widespread use as an antipyretic, analgesic and anti-inflammatory agent. Since then, many nonsteroidal compounds with anti-inflammatory properties have been discovered. Since ASA's introduction in 1897, more than two dozen chemically-related drugs have been developed. The group is generally restricted only to those substances that act by inhibiting components of the enzyme system in the metabolism of arachidonic acid and formation of eicosanoids. Key pharmaceutical class is that of NSAIDs, which act on the metabolism of arachidonic acid, reducing the production of prostaglandins that intervene on the vascular phase of inflammation and sensitize nociceptors by lowering the activation threshold by algogenic substances. Prostaglandins' synthesis part from phospholipids commonly contained in the membrane structure of all cells, which, by enzymatic action effect of phospholipase, is transformed into arachidonic acid: this molecule acting on the cyclooxygenases 1 and 2 (Cox-1 and Cox-2), which are responsible for the synthesis of PGs. PGs, in turn, act on the prostaglandin receptors (EP) and this activation is derived from a particular sensitization of nociceptors, able to produce hyperalgesia. Many common drugs used for joint pain, rheumatism, but also fever, act by inhibiting the COX-1 or COX-2, or both, and reducing, among other things, pain and hyperalgesia. The COX binds the NSAIDs on an arginine residue (ARG120) and from here the inhibitory part of the drug clutters the active site of "enzyme; in fact the" enzyme is bifunctional and has two active sites, one that transforms the "acid in PGG₂ and another that turns this" last in PGH₂, but NSAIDs inhibit the first of the two sites. It is a reversible competitive inhibition, with the exception of aspirin, which binds instead to Serina 530 with an irreversible bond. Its effect, therefore, lasts even after the deletion of the medication from body, as long as it is not synthesized new enzyme. The various NSAIDs, presently, can be divided on the basis of their selectivity to COX.

The COX-1 is a constitutive enzyme expressed in most cells, responsible for the physiological production of prostanoids, ubiquitous mediators that, through the interaction of specific membrane receptors coupled with G proteins, are involved in intercellular communication and in the modulation of several homeostatic functions (gastric, platelets, kidney).

COX-2 is inducible isoform of the enzyme as a result of pro-inflammatory stimuli, mainly responsible for the production of prostanoid mediators of inflammation and in pain transmission. However, in the CNS, kidney, prostate, testes, and vessels are COX-2 of constitutive type. Inhibition of COX-2 by NSAIDs, should be responsible for the therapeutic effects, whereas inhibition of COX-1 would result in adverse reactions to these drugs. The COXIB are selective inhibitors of COX-2.

NSAIDs are classified as in **Figure 2**.

It was estimated that about 100 million people worldwide use NSAIDs and therefore are the most widely used drugs ever, especially in the treatment of postoperative pain and pain related to musculoskeletal disorders (Berde and Sundel) such as rheumatoid arthritis or osteoarthritis [14].

Diclofenac has anti-inflammatory analgesic and antipyretic effect, and its power is greater than other NSAIDs. It is indicated for chronic inflammatory diseases such as rheumatoid arthritis and osteoarthritis at a dose of 100–200 mg/day. It is also used as analgesic in the case of musculoskeletal injuries, tendinitis, postoperative pain, and dysmenorrhea (50 mg). It is rapidly absorbed after oral administration and has a short half-life of 1–2 hours. A new salt of diclofenac, diclofenac epolamine, is highly effective as both an anti-inflammatory and an analgesic agent for its favourable permeation characteristics. Furthermore, recently, it is put commercially a new formulation of diclofenac injectable, diclofenac sodium together with cyclodextrins, which improves the solubility of diclofenac. It is a new pharmaceutical form in 1 ml volume which offers not only the unique advantage of the subcutaneous administration (besides the “classical” intra-muscular injection) but also the use of the lowest dosage.

Ketorolac (LIXIDOL, Toradol): It is a potent analgesic and a moderate anti-inflammatory. Unlike opioid analgesics, it does not give tolerance, dependence, and respiratory depression. It uses intramuscular (30–90 mg) for the treatment of post-operative pain as an alternative to opioids.

It acts in the reduction of post-surgical pain (arthroplasty, disc herniations, femoral fractures with reduction). It is also used in the most difficult forms of dysmenorrhea, or for the treatment of renal colic sporadic and chronic.

| | | | |
|---|--|--|--|
| Salicylates <ul style="list-style-type: none"> • Acetylsalicylic acid (aspirin) • Amoxiprin • Benorylate/Benorilate • Choline magnesium salicylate • Diflunisal • Ethenzamide • Faislamine • Methyl salicylate • Magnesium salicylate • Salicyl salicylate • Salicylamide | Arylalkanoic acids <ul style="list-style-type: none"> • Diclofenac • Aceclofenac • Acemethacin • Alclofenac • Bromfenac • Etodolac • Indomethacin • Nabumetone • Oxametacin • Proglumetacin • Sulindac • Tolmetin | 2-Arylpropionic acids (profens) <ul style="list-style-type: none"> • Ibuprofen • Alminoprofen • Carprofen • Dexibuprofen • Dexketoprofen • Fenbufen • Fenoprofen • Flunoxaprofen • Flurbiprofen • Indoprofen • Ketorolac • Loxoprofen • Naproxen • Oxaprozin • Pirprofen • Suprofen • Tiaprofenic acid | N-Arylanthranilic acids (fenamic acids) <ul style="list-style-type: none"> • Mefenamic acid • Flufenamic acid • Meclofenamic acid • Tolfenamic acid |
| Pyrazolidine derivatives <ul style="list-style-type: none"> • Phenylbutazone • Ampyrone • Azapropazone • Clofezone • Kebuzone • Metamizole • Mofebutazone • Oxyphenbutazone • Phenazone • Sulfinpyrazone | Oxicams <ul style="list-style-type: none"> • Piroxicam • Droxicam • Lornoxicam • Meloxicam • Tenoxicam | [COX]-2 inhibitors <ul style="list-style-type: none"> • Celecoxib (FDA alert) • Etoricoxib (FDA withdrawn) • Lumiracoxib TGA cancelled registration • Parecoxib FDA withdrawn • Rofecoxib (withdrawn from market) • Valdecoxib (withdrawn from market) | |

Figure 2. Classification of NSAIDs.

Treatment with ketorolac should not exceed 5 days to the possibility of serious complications gastric, haemorrhagic, and renal.

Ibuprofen (Brufen, MOMENT) is used as anti-inflammatory for rheumatoid arthritis, osteoarthritis, peri-arthritis, low back pain, sciatica at a dose of 2400 mg/day. At lower doses, it is devoid of anti-inflammatory activity and is used as an analgesic in various forms including painful headache and dysmenorrhoea (400 mg every 4–6 hours).

It has a short half-life of 1–2 hours; it is highly bound to plasma proteins and it does not interact with anticoagulants.

Naproxen (ALEVE, FLOGINAX, Naprosyn, Naprosyn GEL, NAPRIUS, MOMENDOL, SYN-FLEX). It has the same pharmacological profile and the same indications of ibuprofen. It is a well-tolerated drug. It has long half-life of 12–15 hours. The half-life is approximately doubled in elderly patients thus making it necessary dosage changes.

Ketoprofen (Fastum, Orudis): It inhibits both COX and LPX. This property does not make it superior than others NSAIDs. The efficacy of ketoprofen in the treatment of rheumatoid arthritis and osteoarthritis is similar to that of aspirin and other NSAIDs. It has a very short half-life of 1–2 hours; it is highly bound to plasma proteins, but does not modify the activity of warfarin and digoxin. Probenecid increases the plasma levels and prolongs the half-life [15].

The World Health Organization (WHO) in 1996 proposed a scale for pain assessment in the first instance oncological and later adopted as a guideline for the pharmacological treatment of musculoskeletal pain. This scale consists of three levels:

- Pain Mild (assessment of pain according to visual analogue scale—VAS from 1 to 4): it is suggested treatment with NSAIDs or acetaminophen ± adjuvants.
- Pain Mild to moderate (VAS 5-6): it is suggested treatment with weak opioids or NSAIDs ± paracetamol ± adjuvants.
- Pain Severe or moderate to severe (VAS 7-10): it is suggested treatment with strong opioids ± NSAIDs or acetaminophen ± adjuvants [16] (**Figure 3**).

The chronic use of NSAIDs cause: coagulopathies (reduced platelet aggregation, increased bleeding time), gastrointestinal toxicity (gastritis and dyspepsia, ulcers, vomiting blood, diarrhoea), hepatotoxicity (increased transaminases, cholestatic hepatitis, acute hepatic necrosis), haematological effects (leukopenia, agranulocytosis, aplastic anemia), kidney effects (salt and water retention, azotemia, oliguria, interstitial nephritis, papillary necrosis, acute), respiratory effects (bronchospasm), allergy, dermatitis, headache.

NSAIDs interactions with other drugs: reduce the efficacy of beta-blockers, ACE-inhibitors and diuretics; increase the effect of sulfonyleureas and toxicity of aminoglycosides and cyclosporine. The COXIB, long-term, increases the risk of serious cardiovascular events and thrombosis, myocardial infarction, stroke; also, such as NSAIDs, increase the risk of serious gastrointestinal adverse effects (bleeding, ulceration and perforation), even in the absence of warning symptoms [17].

| | | |
|--|--|--|
| <p>Mild Pain (VAS 1–5)</p> <ul style="list-style-type: none"> • Acetaminophen 1 g q6h • NSAID (if not contraindicated) • Codeine 30–60 mg q6h or • Tramadol 50–100 mg q6h | <p>Moderate Pain (VAS 6–7)</p> <ul style="list-style-type: none"> • Acetaminophen 1 g q6h and • NSAIDs (regular) (if not contraindicated) and • Codeine (regular) and/or • Tramadol 50–100 mg q6h and/or • Morphine 0.1–0.2 mg/kg q4h and/or • PCA/nerve block/ neuroaxial blockade | <p>Severe Pain (VAS 8–10)</p> <ul style="list-style-type: none"> • Morphine (regular or continuous) and • Acetaminophen 1 g q6h and • NSAIDs (if not contraindicated) and/or • PCA/nerve block/ neuroaxial blockade |
|--|--|--|

Figure 3. The World Health Organization (WHO) scale for pain assessment in the first instance oncological and later adopted as a guideline for the pharmacological treatment.

To minimize or abolish the adverse effects of the oral administration of these drugs, there are several techniques used in physical and rehabilitation medicine, such as mesotherapy, iontophoresis, phonophoresis, and last but not least, phytotherapy which uses natural substances with anti-inflammatory properties.

3. Antalgic and rehabilitative mesotherapy

Mesotherapy is based on the principle that intradermal therapy produces a “micro deposit” of the drug in the dermis which is then slowly released into the surrounding tissues. Nowadays, mesotherapy should be considered an increasingly important aspect of Interventional Physical and Rehabilitation Medicine (IPRM).

Mesotherapy consists of a series of “microinjections” of drug/active substance into the dermis using short needles where the needle is positioned at an appropriate angle depending on the thickness of the skin. A French physician, Michel Pistor, reporting encouraging results with small drugs administered intradermally to patients with a variety of clinical condition. He defines mesotherapy as a novel analgesic therapy for a variety of rheumatologic disorders [18, 19]. The term mesotherapy derives from Greek (Mesos = “Medium” and Therapeia = “care”), and refers to the mesoderm germ layer from which are differentiated tissues and structures such as bone, cartilage, muscle and connective tissue. It makes superficial injections directly on the area above the structure affected by the disease, using a 27–33 gauge needle; typically administered are 0.10–0.20 ml of medication and injection points at 2–3 cm distance.

Although the fundamental principles upon which mesotherapy are those expressed by Michel Pistor, mesotherapy concept evolved in recent years: from the concept of needle insertion in the point of greatest pain (such as trigger points) to injection of analgesic agents such as lidocaine or bicarbonate, [20, 21] arriving at the concept of mesotherapy as aspect of Interventional Physical and Rehabilitation Medicine (IPRM). The Interventional Physical and Rehabilitation Medicine (IPRM) is the possibility by physiatrist to insert in the individual rehabilitation project, with the most appropriate timing, an interventional procedure to support the conservative applied methods. In addition, mesotherapy is a procedure in which not only is it possible to introduce a specific drug, but it represents the possibility to choose whether to treat the point of maximum pain, the area of referred pain or functional damaged district. Depending on the needle technique used, it is possible to reach different tissues and different depths. The use of more deep techniques, associated with the administration of the drug, can interrupt the inflammatory cascade and it generates, as a result of the mechanical action of the needle, tissue repair processes with reduction of local fibrosis.

There are various techniques of mesotherapy that are different depending on the used needle length and gauge, the injected substance, the depth of penetration:

Intraepidermic (IED) in which the injection is carried out at the level of the epidermis-dermis junction at 1–2 mm depth with the needle parallel to the skin and the bevel of the needle faces upwards.

Nappagein in which is recommended a deeper injection at 2–4 mm with an angle of 30–60 degrees. Usually two to four injections are carried out with a space of 3–4 mm between each point of injection.

Point-by-point (PPP) with a deep injections at 4 mm at most.

Mesoperfusion in which injections should be involved at 4–13 mm over 30–90 minutes.

The perfect drug for mesotherapy is the one whose technical data sheet covering three routes for parenteral administration. If a certain drug or association exists both intramuscular and intravenous version, the first is preferred, because the tissues of mesotherapy—epidermis, dermis and subcutaneous—have greater histochemical affinity with muscle rather than blood.

The most commonly used in mesotherapy drugs are NSAIDs (diclofenac, ketoprofen, aspirin, ketorolac, piroxicam), muscle relaxants (thiocolchicoside, pridinolo mesylate), vasoactive drugs (mesoglycan), calcium chelators (EDTA) and local anesthetics (lidocaine, procaine). Diclofenac sodium together with ciclodextrins is a solution for injection can be administered intramuscularly or subcutaneously as mesotherapy. It can be used in different doses: in case of mild or moderate pain, it is sufficient to use the lowest dose (25 mg). A dose of 50–75 mg may be required in case of severe pain. Exceptionally and in severe cases, it can be administered a second dose of 75 mg after six hours. The maximum daily dose (24 hours) must not exceed 150 mg.

They should never be injected mesotherapy turbid drugs or frankly precipitating, since the crystals also of small size can obstruct thin blood capillaries and determine thrombosis and tissue necrosis. To avoid the reaction of acid-basic cocktail with opposite pH products, you

can load the syringe with the defined quantity of saline at the beginning of the preparation. Each cocktail drug must be diluted in physiological solution in the volumetric ratio of 1:10 or 0.5 ml:5 ml. In mesotherapy it is prohibited inject oily and alcoholic solutions for the high risk of necrosis. Corticosteroids are contraindicated both individually and in cocktails because it can cause skin atrophy. In the case of extra-articular injections it is a side effect with estimated frequency from Brinks et al. [22] of around 1%, but with possible serious aesthetic impact, which in intradermal injections is likely much higher [23].

The risk of allergic reactions preclude the intradermal administration of a muscle relaxant plus a nonsteroidal anti-inflammatory agent in the same syringe as it is not possible to determine which drug has caused the allergy.

Protocols for mesotherapy allow to make one or more cycles depending on the symptoms, the severity of the disease and the patient's response. In chronic painful conditions there are three distinct phases: attack (sevently weekly treatments are administrated), control (four fortnightly treatments are given to confirm results and prevent short-term recurrences) and maintenance phase (monthly or seasonal treatment). In resistant pain, twice weekly therapy is recommended in the "attack phase" depending on the analgesic effect obtained. There are several advantages of mesotherapy: the process of introducing needles into the skin stimulates a reflex action thereby increasing endorphin levels, which blocks the painful sensation; the rapidity of action, related to the short time required to reach the site of action, as well as a prolonged local effect and a reduction of side effects.

The use of mesotherapy in Italy was approved by the Italian Society of Mesotherapy (SIM) in 1975, following a number of multi-center studies have confirmed the effectiveness of this method in the control of joint pain (hip/knee osteoarthritis/Hand, neck pain, back pain, tendonitis) (**Figure 4**).

In addition to the analgesic and anti-inflammatory effect, these studies have demonstrated the safety of administration and reduction of side effects compared to oral via.

The combined use of mesotherapy with physical therapy achieves a synergistic effect in muscle injuries of athletes, control of neuropathic pain, inflammatory tendonitis, degenerative and/or calcified. The indication more appropriately, according to these studies, is treatment of musculoskeletal and osteo-articular pain. Open studies conducted with mesotherapy approach in musculoskeletal pain such us arthritis, neck pain, lower back pain, and tendinopathy show a reduction of pain at least 50% compared to pre-treatment [24–39].

Furthermore, literature reported that a great number of patients treated with mesotherapy for musculoskeletal pain disorders had rapid pain relief, generally when the patient responds within the first three sessions of therapy [40].

Costantino et al., started a study with the aim to compare mesotherapeutic versus conventional systemic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in patients with acute low back pain. They showed that the administration of NSAIDs and corticosteroids via mesotherapy can provide the same therapeutic benefit as that induced by conventional (oral and intramuscular) drug administration. The major aspect is the comparable effectiveness of mesotherapy and conventional systemic therapy, despite the lower

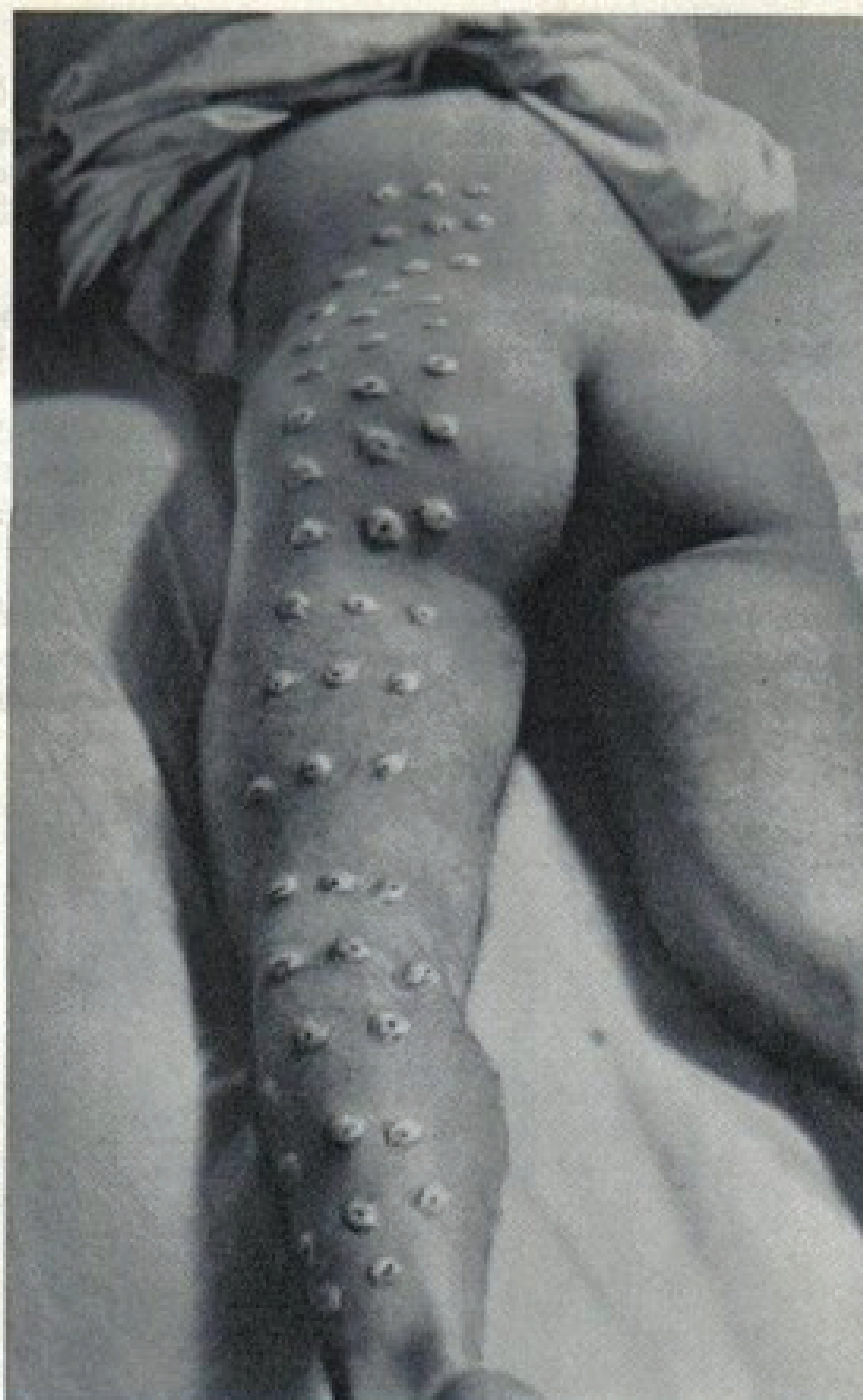


Fig. 113. — Sciatique gauche. 2 à 3 cc. d'Algipan sont répartis tout le long du trajet sciatique douloureux.

Figure 4. Mesotherapy in 1975, low back pain and sciatica.

amount of drugs administered to patients undergoing mesotherapy (41.67% ketoprofen and 50% methylprednisolone). Author concluded that subcutaneous drug administration results in a very slow drug absorption such as intramuscular and oral and that it could be assumed

that anti-inflammatory substances, dispensed with mesotherapy, reach a high drug concentration into the subcutaneous tissue and it acts locally close to the inflammatory cells, sensitive fibers and vascular mediators that generate inflammation and pain [41].

Even in the case of carpal tunnel syndrome, diagnosed by clinical examination and neurophysiological investigation, it used a mixture containing lidocaine 10 mg, ketoprofen lysine-acetylsalicylate 80 mg, xantinol nicotinato 100 mg, cyanocobalamin 1000 mcg more injectable water, injected above the transverse carpal ligament, at the base of the thenar and hypothenar eminence. It has noticed already after 24 hours, a significant reduction in pain and paresthesias, which lasted up to 12 months in over 50% of the sample.

The mesotherapy with NSAIDs is applicable to several pathological conditions, as demonstrated by several studies, starting from pes anserine bursitis, treated by Saggini et al. (Figure 5) with nine sessions of mesotherapy with diclofenac sodium (25 mg/1 ml; Akis, IBSA, Switzerland), 1 ml per session, three times a week. These patients' outcome was assessed by visual analogue scale (VAS), along with the ability to perform activities of daily life, the ability to participate in sports, level of pain, symptoms, and quality of life. These measurements were performed before and after the treatment period and at 30 and 90 days of follow up. It was thus obtained with a significant reduction in pain after the treatment period; further

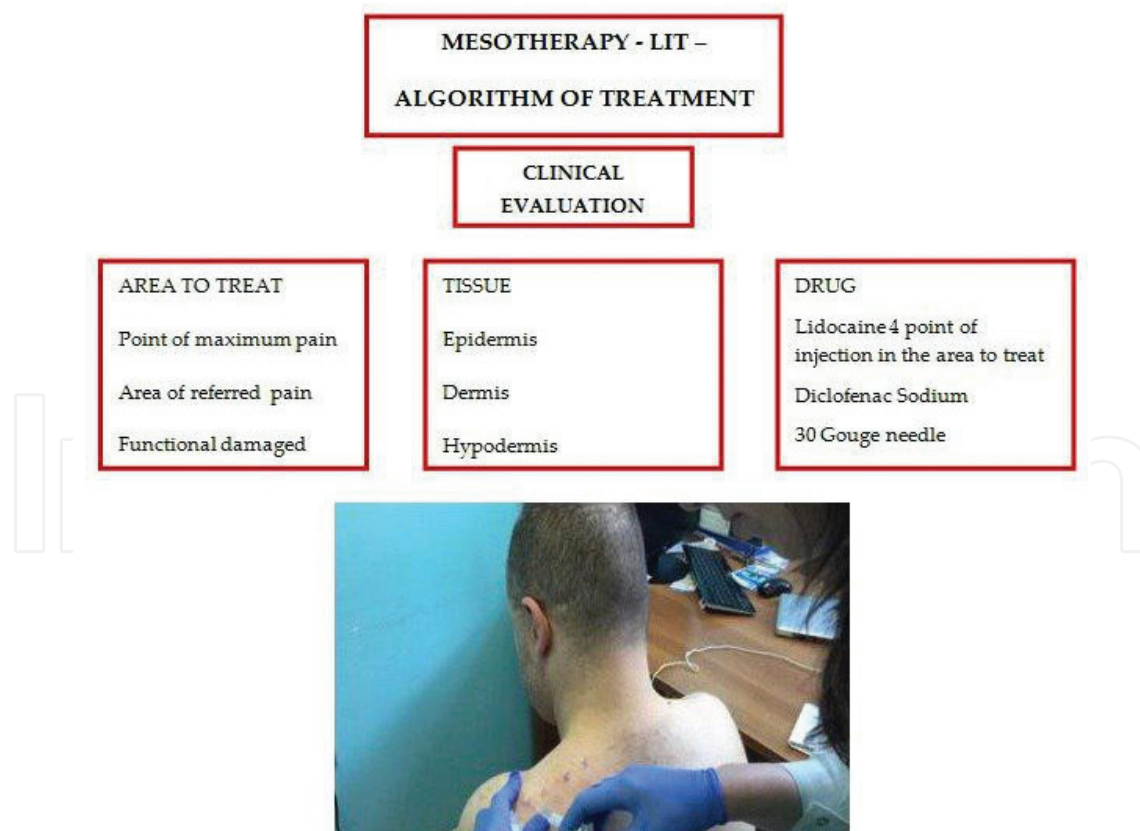


Figure 5. Algorithm treatment of antalgic and rehabilitative mesotherapy. Center of Physical and Rehabilitation Medicine, "Gabriele d'Annunzio" University, Chieti- Chief R. Saggini md.

ultrasound investigations showed a hypoechoic area reduction related to pes anserine bursitis only in the group receiving mesotherapy and not in the control group, treated, however, with oral therapy [42].

The mesotherapy is therefore an innovative technique specific of Interventional Physical and Rehabilitation Medicine (IPRM). It enables operation of painful conditions also chronic, inflammatory, degenerative, and traumatic diseases. This type of therapy, which can be defined “ecological,” fits perfectly into the global bioprogressive approach, where to work on the bone-myofascial system, this must be put in the control condition and reduction of pain, to optimize dynamics of the body and thus increase performance.

4. Iontophoresis

The method of iontophoresis has been described by Pivati in 1747. In the eighteenth century, two illustrious scientists Galvani and Volta, joined together the principle by which electrons’ movement generate electricity and that according to which electricity moves ions [43] (Figure 6). In the 1870s, the German Hermann Munk (1839–1912) extensively investigated the current mediated transport of substances, such as strychnine, through porous membranes. He then thought about transmitting drugs through intact human skin as the skin is some kind of a porous membrane as well. The strychnine experiments were repeated by the French physician

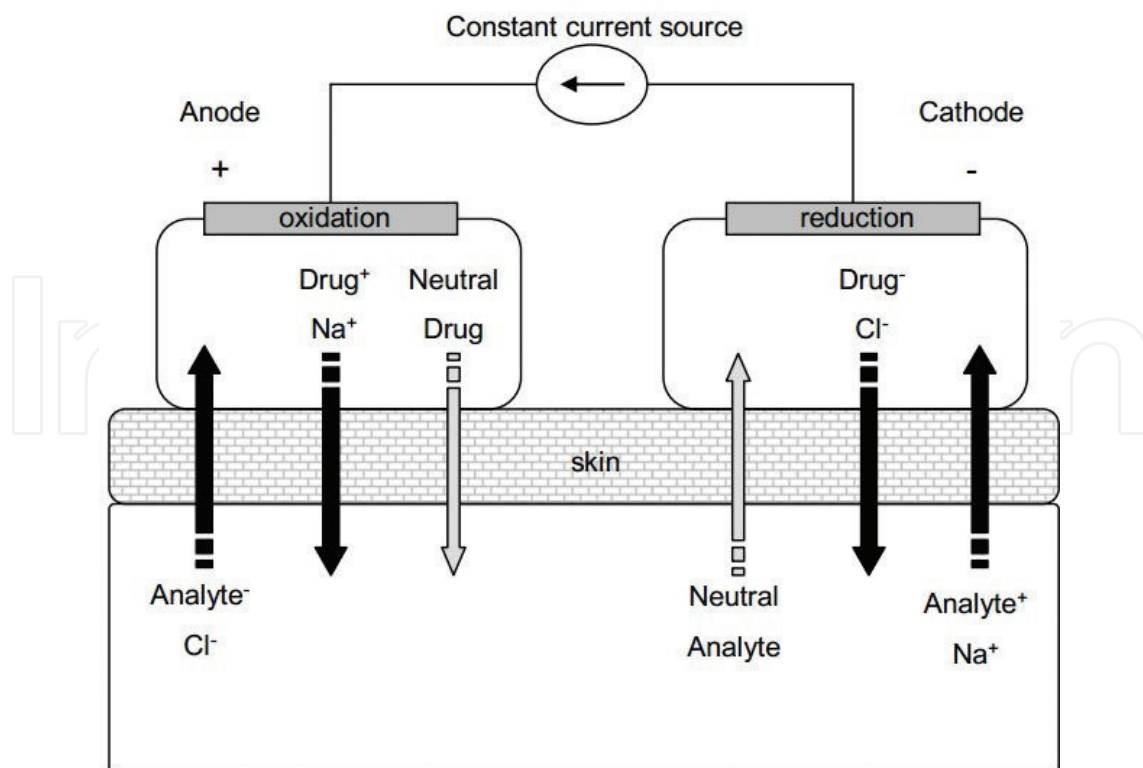


Figure 6. Molecular transport during iontophoresis.

Stéphane Leduc (1853–1939), showing that strychnine sulfate is transported from the positive to the negative pole of the electric circuit.

This phenomenon was intensively studied by Fritz Frankenhäuser (born 1868) who invented the term “Iontophorese” earlier than 1908 [44].

Iontophoresis is applied in physical medicine to treat musculoskeletal disorders such as osteoarthritis, bursitis, and tendinopathy by transdermal drug administration. It is a procedure that uses the application of a constant voltage electricity to convey through the skin charged and highly polar molecules. Iontophoretic transport can occur by electrorepulsion or electromigration, but considering the properties of the skin, drug can be transported by electro-osmosis [45].

The migration of the therapeutic agent also depends on its charge: cationic or neutral substances are conveyed toward the anode, anionic substances are conveyed toward the cathode. Applying a low voltage current, following the principle dell'elettro repulsion, the ions are repelled through the skin. Since the skin is negatively charged under physiological conditions, the electroosmotic flow is then from anode to cathode [46].

Restrictions about iontophoretic system, include law limits on the amount of current that can be used in humans (nowadays set to 0.5 mA/cm²) and the irreversible harm that such currents could do to the skin's barrier properties. Furthermore, iontophoresis has not managed to significantly improve the transdermal vehiculation of molecules >7000 Dalton [47].

The limit of molecular size can be overcome with electroporation, i.e., the application of high voltage pulses to induce modifications of skin.

Electroporation uses high voltages (≥ 100 V) for short treatment periods (milliseconds), which increase the skin permeability, probably for the generation of transient pores during electroporation. The result of electroporation is not always better than iontophoresis, but appears lasts longer. It depends on the energy of the electrical field [48]. (**Figure 7**)

Many factors influence the outcome of the transdermal delivery of drugs: physicochemical properties of the substance (charge, concentration, size of molecules), formulation (pH, viscosity, presence of other ions), biological variation (age, sex, site of application, vascularization), body temperature, types of electrodes and current used, duration of the session. (**Table 1**)

The main advantage of the transdermal administration of drugs, is the increased bioavailability of the active principle in absence of hepatic first-pass metabolism [49]. This hypothesis was tested for numerous NSAIDs in both in vitro and in vivo studies [50, 51]. In vitro, it has been demonstrated that piroxicam gel solution diffusion through the skin is 100–1000 fold higher applying iontophoresis for 6 hours, compared to the passive diffusion [52].

Also in vivo on man, it has been demonstrated this advantage of iontophoresis and it has been noticed a concentration of piroxicam in the stratum corneum significantly higher compared to the passive diffusion [53]. In another study in vitro, ketorolac has been conveyed through rat skin applying a current density from 0.11 to 0.15 mA/cm² with 10–100 fold increase than its passive vehiculation [54]. (**Figure 8**)

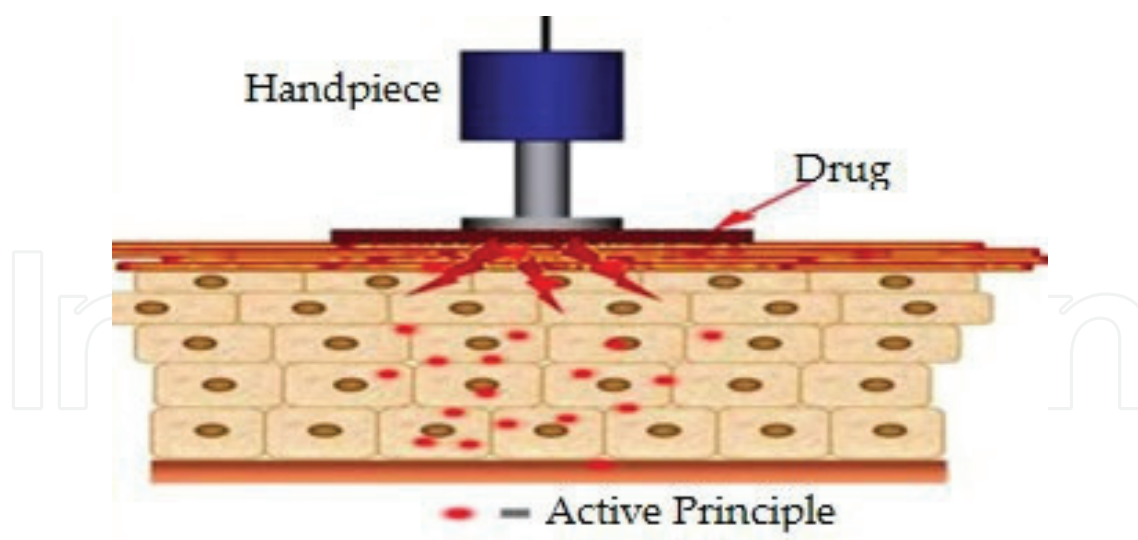


Figure 7. Electroporation.

| Drug | Polarity |
|---------------------------|----------|
| Lysine acetylsalicylate | Negative |
| Diclofenac sodium | Negative |
| Indomethacin | Negative |
| Piroxicam | Negative |
| Ketoprofen | Negative |
| Benzydamine hydrochloride | Bipolar |
| Methyl nicotinate | Positive |
| Phenylbutazone | Positive |
| Glycol salicylate | Positive |

Table 1. Polarity of NSAIDs.

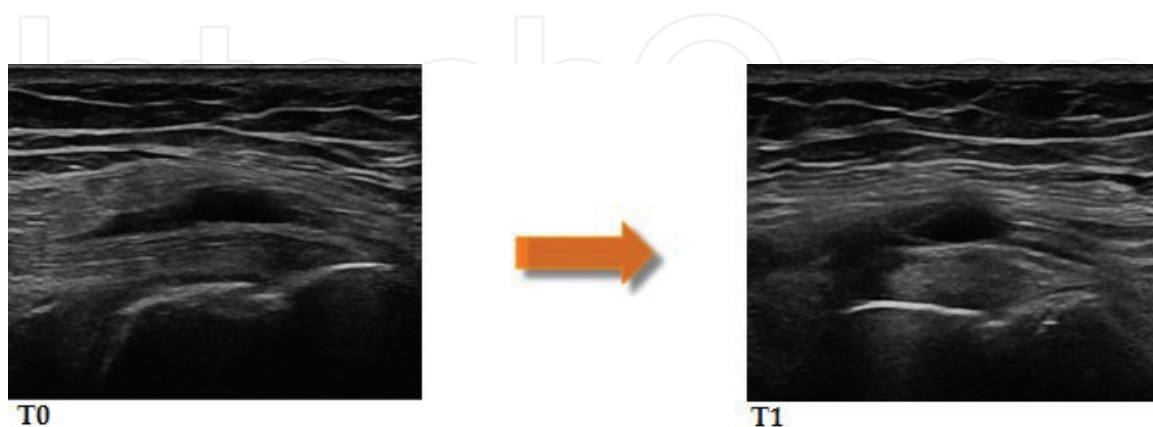


Figure 8. Ultrasonography: reduction of a hypoechoic area (pes anserine)—pre (T0) and after (T1) the treatment period: 30 days of transdermal diclofenac sodium 25 mg/ml with electroporation(Isofor Compact) for three times a week for three weeks with sessions lasting 20 minutes each. Center of Physical and Rehabilitation Medicine, “Gabriele d’Annunzio” University, Chieti- Chief R.Saggini MD.

A series of studies reported anti-inflammatory effects of iontophoresis and electroporation in many common inflammatory conditions of the musculoskeletal system. All of the clinical investigations demonstrated at least positive clinical outcome [55–58].

One of the first studies on the transdermal drug delivery goes back to 1996 by Saggini et al. in the treatment of rheumatic pain with ketorolac compared with placebo. Seven days after the end of therapy, patients who received ketorolac have experienced a further reduction in pain (highly significant compared to pre-treatment values; $P < 0.005$). The best results were observed in patients who had severe or very strong pain at the beginning of treatment. The intensity of pain in patients who received placebo, returned to pre-treatment values [59].

Baskurt et al. conducted a study comparing the effectiveness of transcutaneous delivery of naproxen via iontophoresis versus phonophoresis. The results suggest that iontophoresis and phonophoresis of naproxen are equally effective electrotherapy methods in the treatment of lateral epicondylitis [60].

Demirtaş et al., suggest positive effect of iontophoresis in the treatment of lateral epicondylitis and indicate that iontophoresis of sodium diclofenac is more effective than that of sodium salicylate [61].

The effectiveness of this therapeutic method has also been tested in secondary painful events in arthritic disease of the spine. Patients were treated with diclofenac sodium and betamethasone for 20 minutes and evaluated immediately after the end of the treatment and after 24 hours, by detecting a significant reduction of spontaneous pain after the application, which is maintained unchanged even at 24 hours [62]. Also in subjects with inflammatory disease, iontophoresis returns excellent results, as observed in subjects with inserted pes anserine bursitis in a study, the purpose of which was to compare the efficacy of conventional oral therapy with anti-inflammatory, mesotherapy and (Isofor Compact) electroporation using the same substance. In all groups, we were obtained with similar results in terms of decrease in pain and improvement in quality of life at the end of the third week of treatment. However, the ultrasonography showed a hypoechoic area reduction of pes anserine bursitis only in the groups treated with mesotherapy and electroporation [63].

Moreover, iontophoresis appears a safe and applicable method in a complex rehabilitation project, also in children, as in the case of osteochondrosis of the tibial tuberosity, inflammatory degenerative disease. The results showed a significant reduction in pain even after the first two weeks of treatment and pain relief in its third week. A significant improvement in the ultrasound examination at the end of the protocol with normalization of the patellar tendon thickness and peritendinous edema resorption, a symmetrization of the load at podobarometric examination and a significant improvement in the isokinetic test [64].

5. Phonoforesis

Another interesting method of treatment of Psychiatric and Rehabilitation Medicine is the phonophoresis, that consists in the use of ultrasound for transcutaneous drug delivery.

Cutaneous bioavailability in most of the marketed dermatological formulations is low.

The skin represents a significant barrier to the entrance of foreign substances, but is also a potential therapeutic away.

The stratum corneum has a structure in determining barrier function. The corneocytes (about 85% of the mass of the stratum corneum) and intercellular lipids (15%) are arranged in about 15–20 layers [65]. It consists of approximately: 70% protein, 15% lipids, and only 15% of water [66]. In corneocytes, thickened keratin and filaggrin and cleavage products are present. The corneocytes is rich in protein and is surrounded by lipids [67]. Weight ratio of 50% ceramides, 35–40% cholesterol, fatty acids liber10–15% contained within the extracellular spaces and arranged in double layer slats make the stratum corneum impermeable to water soluble substances [68].

Changes of this lamellar structure and/or of its lipid composition constitute the biochemist and structural basis of permeability variations related to the body site.

It is possible to increase the penetration of active substances through the stratum corneum using ultrasound, reaching, thus, the area to be treated with the appropriate concentration of drug at a certain depth and in a selective way, without dispersion in bloodstream and first pass effect [69]. Ultrasound (US) produces alterations in the structure of the stratum corneum and increases the permeability [70]. (**Figure 9**)

Temperature increase induced by the US increases the kinetic energy of drug's molecules, dilates the points of entry through the skin (hair follicles and sweat glands), and increases the blood flow in the treated area [71]. US also produce mechanical effects as microstreaming and cavitation of cells, or in any case nonthermal effects as reduction of the membrane potential, alterations of lipid structure, with increased cell permeability and ionic conductance [72].

Cavitation refers to the formation and collapse of small air bubbles formed in a liquid due to a pressure change induced in the tissue fluid from the passage of ultrasound. (**Figure 10 a - b**)

Cavitation can be stable (when ultrasound of high intensity and low frequency passing through a liquid, produce small bubbles that oscillate rhythmically in size) or unstable (when high-frequency ultrasound generate bubbles that grow and collapse abruptly). (**Figure 10 c - d**)

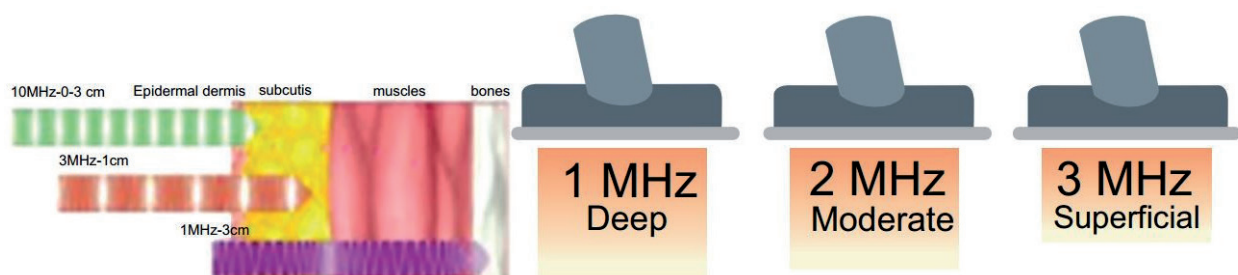


Figure 9. Ultrasound characteristics.

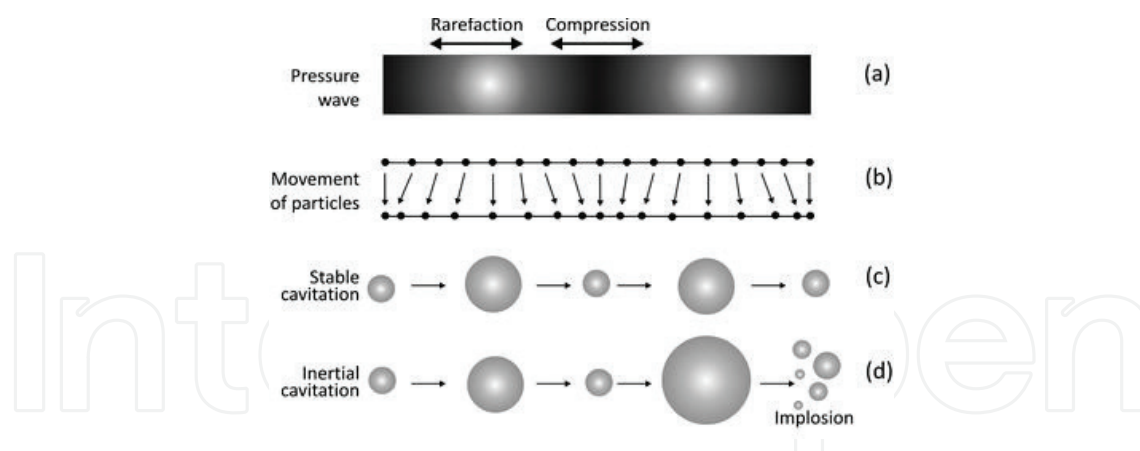


Figure 10. Cavitation phenomenon.

For microstreaming, it means the formation of vortices in small volumes of cytoplasmic and interstitial fluid; this improves the dissolution of the drug particles in suspension and alters the cell membrane structure by setting the permeability to sodium and calcium ions [73].

For a long time, effective frequencies have been investigated to produce therapeutic effect.

Ultrasound for therapeutic purposes, are used in physical and rehabilitation medicine with a range between 0.75 and 3 MHz: lower frequencies penetrate most deeply (3–5 cm) and are preferred in subjects with a high percentage of body fat, while higher frequencies are absorbed from superficial tissues (1–2 cm) (**Figure 11**).

In rehabilitation, phonophoresis is used to convey drugs such as corticosteroids and NSAIDs to treat diseases affecting the musculoskeletal system, such as osteoarthritis treated by Boyaci et al. with 100 mg of ketoprofen using an applicator 5 cm in diameter, with a frequency of 1 MHz, with a power of 1.5 W/cm² for 8 min. Patients involved in the study were assessed before and after treatment with VAS scale, 15-m walking time, and Western Ontario and McMaster Universities Arthritis Index (WOMAC), and reported a significant improvement in their condition [74]. Also a study of Tascioglu et al. showed greater efficacy of pulsed mode than continuous mode in the treatment of osteoarthritis of the knee [75].

Luksurapan has instead used 20 mg of piroxicam in continuous mode, power, 1.0 W/cm² in sessions from 10 minutes to treat the same disease, obtaining excellent results in particular relating to the VAS scale [76].

Another disease that can be treated with phonophoresis is the painful myofascial syndrome, treated with diclofenac gel (Voltaren emulgel) applied with an applicator 5 cm in diameter at 1 MHz of frequency and power 1.5 W/cm² for 10 minutes on two trigger points of the trapezius muscle, with improvement in pain compared to the baseline condition [77].

For temporomandibular joint (TMJ) pain phonophoresis with 1.0 MHz frequency, power 0.8 to 1.5 W/cm² in continuous mode for 15 minutes was applied, with results suggesting that transdermal delivery of indomethacin with US has significant effect on the TMJ pain [78].

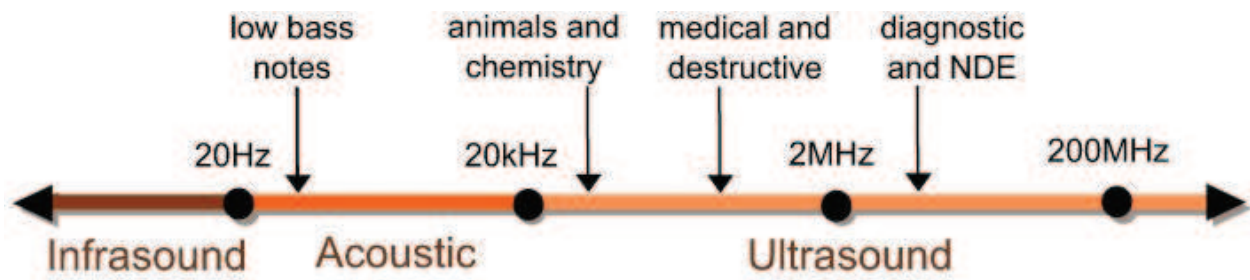


Figure 11. Frequencies of ultrasound and application area.

Another experience is related to use of phonophoresis with ultrasound of high intensity and low frequency passing through the skin (hair follicles and sweat glands) with addition of an anti-inflammatory phytotherapy gel in treatment of Biceps Long Head tendinitis in rotator cuff disease compared to a Extracorporeal Shock Wave Therapy (ESWT) treatment of the rotator cuff tendinitis.

At the present time, there are no specific and standard protocols for the application of ultrasound to the transdermal drug delivery, because of multiple variables of treatment such as frequency, method of delivery, molecular structure of the drug, patients' age, thickness, and hydration of the skin.

It is definitely a treatment that offers advantages compared to the oral administration of anti-inflammatories.

Despite the contradictions in the various studies on mode of administration, frequency and drug use, almost all agree on the effectiveness of this therapeutic method in relieving pain and restoration of function that is impaired in different conditions affecting the musculoskeletal system [74].

6. Phytotherapy

Acute and chronic diseases of the musculoskeletal system represent about 40% of health demands. If you add to this the progressive increase in the average lifespan resulting in increased incidence of mechanical, metabolic and consumption alterations, that are the basis of chronic myofascial and joints' diseases, it understands the interest toward an "complementary medicine." In this context, phytotherapy and the search for natural substances that act on inflammation and pain fit perfectly.

Inflammation is a response model to the damage; it leads to accumulation of cells and exudates in tissues harmed in to protect from further damage. Inflammation has been studied for thousands years to try to counteract the effects it has on the human body [79].

Phytotherapy is the use of plant-derived medications in the treatment or prevention of more inflammatory and noninflammatory diseases. Indeed medical herbalism which is characterized by an empirical approach, phytotherapy is a science-based medical practice. Numerous

trials and pharmacological studies of specific phytotherapeutic preparations exist. In some countries, it is considered sufficient to license phytotherapeutic products as medicines, whereas in other countries, phytotherapy is viewed as a form of traditional medicines.

The concept of phytotherapy was originated by French physician Henri Leclerc, who first used the term in 1913 and who published various editions of the *Précis de phytothérapie* the first in 1922. Successively, in 1934, the term Phytotherapy was used in common as a definition by Eric Frederick William Powell, an English expert of herbalism. Only in 1960, a German herbalist and physician Rudolf Fritz Weiss published *Lehrbuch der Phytotherapie* (1960; Herbal Medicine), which determined a definition of this topic in all Europe [80].

Only in the 1980s, the scientific research published in scientific article (as in journal *Phytotherapy Research*) with a definition in the medical-scientific field of phytotherapy began.

A commonly used in phytotherapy is standardization, which is the need to have a minimum of one or more active compounds or groups of plant extract compounds.

Natural products with anti-inflammatory activity have long been used as a folk remedy for inflammatory conditions such as fever, pain, migraine, and arthritis. The report of the British Nutrition Foundation offers a classification of phytochemicals useful information on products with anti-inflammatory properties [81].

Extensive scientific research revealed that curcumin has anti-inflammatory action [82].

The anti-inflammatory activity of curcumin is mainly due to the inhibition of arachidonic acid metabolism, cyclooxygenase (COX), lipoxygenase (LOX), interleukin (IL), tumor necrosis factor (TNF) and also due to the stabilization of the lysosomal membrane [83–85].

In the pathogenesis of arthritis sundry inflammatory cytokines (TNF, IL-1, IL-6), phlogosis enzymes (COX-2, 5-LOX, MMP-9) and adhesion molecules have a central role and almost all of this are synthesized following the gene transcription of NF-kB. Joe et al. investigated the effect of curcumin on acid glycoprotein in serum of rats with induced arthritis [86]. Treating inflammation in these rats with arthritis induced with curcumin per os, has been seen a 73% reduction in the levels of Gp A72.

The typical cartilage consumption that occurs in rheumatoid arthritis, is due to the action of matrix metalloproteinases (MMPs), whose MMP-1 and MMP-3 genes are over expressed in synovial fibroblasts of patients affected by this disease rheumatoid arthritis. Onodera et al. [87] have shown that curcumin blocks the upregulation of MMP mRNA.

Furthermore, curcumin can enhance the growth inhibitory and pro-apoptotic effects of celecoxib in synovial cells in OA as noted by Lev-Ari et al [88]. A synergistic effect was observed in the inhibition of cell growth when the cells were exposed to celecoxib combined with curcumin. The inhibitory effect of the combination of these drugs on cell growth resulted in an increase of apoptosis induction. The use of celecoxib at lower concentrations and more secure in combination with curcumin can provide a combination of novel treatment for OA and other rheumatologic disorders.

To relieve symptoms of arthritis is also used Lyprinol, extracted from green mussels from New Zealand, containing triglycerides, sterols, polar lipids and free fatty acids. Lyprinol showed a significant anti-inflammatory activity in induced polyarthritis in rats [89]. The mechanism by which the lyprinolo acts remains unclear. It certainly reduce proinflammatory LTB₄ in human monocytes. Additionally, a human study showed that NZGLM reduces levels of TXB₂, PGE₂ and IL-1 β with a similar power to low doses of omega-3 supplement [90].

The first natural substance used as anti-inflammatory in rheumatoid arthritis and osteoarthritis, was bromelain in 1964 [91]. It is an aqueous extract obtained from stem and fruit of the Pineapple plant. It has several beneficial effects, including the reversible inhibition of platelet aggregation. Currently, it is used mainly in acute inflammation and sports injuries. The anti-inflammatory mechanism is due to increasing serum fibrinolytic activity, reduction in plasma fibrinogen levels, decreasing levels of PGE₂, TXA₂, reduction in bradykinin levels with subsequent reduction in vascular permeability and thus edema; and modulating the adhesion molecules of the immune system cells.

In the treatment of muscle damage, Arnica is also widely used; also known as mountain daisy, mountain tobacco, and leopard's bane, Arnica is a perennial herb of the family Asteraceae [92].

Lyss et al. demonstrated that helenalin, the most active compound from Arnica, inhibits the transcription factor nuclear factor kappa B (NF-kB) through the alteration and stabilization of NF-kB/inhibitor of kappa B complex (IkappaB) in cells T, B cells and epithelial cells and abolish the expression of kappa B gene-driven. Later work showed that helenalin can inhibit the migration and chemotaxis of human neutrophils and activities of 5-lipoxygenase and leukotriene C₄ synthase. As Lyss et al. postulated in 1997, Helenalin indirectly reduces the expression of NF-kB, acting on expression of surface receptors CD25, CD28, CD27, and CD120b that, if occupied, transduce the activation signal for NF-kB [93].

The activation of NF-kB promotes the release of proinflammatory cytokines and the recruitment of local leukocytes, generating pain and phlogosis.

The Arnica ability to inhibit the activation of NF-kB nuclear transcription factors of activated T cells and pro-inflammatory cytokines IL-1b TNF-a are related with their contents, quantity, and quality of sesquiterpene lactones.

When you consider that muscle damage induced by exercise and delayed onset muscles soreness (DOMS) are accompanied by a systemic inflammatory response that is responsible for initiating, amplifying and/or resolving of muscle damage, one can understand why arnica has a role in these situations.

Overall, Arnica (topical and/or oral formulations) showed reproducible clinical benefits, some of which are comparable with anti-inflammatory drugs such as diclofenac [93], ibuprofen, and corticosteroids [94], which are considered the therapy of choice for the treatment of osteoarthritis, postoperative edema, and bruising [95].

The Arnica topical use is supported by studies that prove its effectiveness in reducing the acute muscle pain induced by exercise,[96, 97] and in the symptomatic treatment of osteoarthritis.

Local action is exerted on the muscle, calming the sensation of pain; in the joints, reducing the swelling and pain caused by rheumatic diseases; on the vascular district, reducing hematoma and bruising and protecting blood vessels.

7. Homeopathy

Homeopathy, from the greek ὅμοιος, *omoios*, “similar” and πάθος, *pathos*, “suffering,” was developed in the late 700s by a German doctor, Samuel Hahnemann, in an age when the symptoms were cured with “therapies” often more lethal than diseases, such as bloodletting and enemas. Hahnemann was convinced that the same substance at high doses cause a disease in healthy people, instead, at infinitesimal doses could cure sick people. Also he claimed that diluting especially substances (“potentiation” obtained by the succession of serial dilutions) not only reduced or abolished the toxic effect, but also, paradoxically, increased their curative power [98]. Homeopathy is a pharmaceutical preparation that contains, in equal parts, different homeopathic dilutions prepared from the same tincture [99]. In Italy, homeopathy is regulated by normative reference for homeopathy Legislative Decree of 24 April 2006, no. 219 “Implementation of Directive 2001/83/EC (and subsequent amending Directives) on a Community code relating to medicinal products for human use, as well as the Directive 2003/94/EC. For preparing a homeopathic dilution, in fact, one starts from a basic substance which is then diluted and dynamized. A critical step is the preparation of the mother tincture, whose production technique is described in the French Official Pharmacopoeia (X edition 1983). The ratio between the dried product and water-alcohol mixture is 1:10. The degree of water-alcohol mixture varies in relation to the solubility of the products to be extracted: a plant with predominantly water-soluble active substances is lower with respect to the title of a substance with principles less water-soluble active. It will have to macerate for 21 days, while for an alcoholic tincture it takes 5–10 days. The effects of homeopathic medicines have been studied in numerous study with experimental inflammation [100–103] Homeopathic clinical research has developed over the last twenty years with the increasingly greater use of modern medical methods (clinical trials, observational studies, statistic evaluations, computerized storage programs and instrumental or laboratory testing). For example, *Atropa belladonna* (Belladonna) is commonly used for treatment of local inflammation: it is prescribed for reducing severe pain, inflammation or any infection, especially on the upper part of the respiratory tract. Belladonna is most suitable to treat disorders of the heart, blood vessels, lungs as well as the neuropathic pain. The toxic juice of *Atropa belladonna* in homeopathic formulation is extremely diluted with alcohol in order to eliminate even the slightest trace of toxicity and to remove harmfulness. This procedure makes it suitable for human use [104, 105].

There are three extracts of *Echinacea*: *E. pallida*, *E. angustifolia*, and *E. purpurea* that are proposed as phytoimmunostimulating agents and their activity is mainly directed toward the nonspecific cellular immune system [106] *Echinacea angustifolia* that is used for many years also in traditional medicine, acts in determining an increase of leukocyte activity, stimulation of phagocytosis, TNF production by macrophages and increase of T and B cell activity, as well

as gINF production by lymphocytes [107]. Furthermore, *Echinacea* has antioxidant effects and free radical scavenging capacities, related to the content in polyphenolic compounds. Echinacoside, chlorogenic acid, chicoric acid, cynarine and caffeic acid inhibit the production of free radicals and lipid peroxidation, classic inflammation consequence. All of this caffeoyl derived, are contained in *Echinacea*. Besides, echinacoside induce degradation of type III collagen with a potential role in cicatrization and fibrosys treatment [108]. A series of step-by-step research trial about the biological effects of homeopathic Arnica montana, specially the Arnica montana 6cH, using animal models is presented in literature [109]. Arnica montana is a plant from the family Compositae native of East and Central Europe hills. Leaves, flowers, and roots contain tannins, flavonoids, lactones sesquiterpenic, alcohols and obviously helenalin which is the active principle best known [110]. It acts inhibiting the transcription factor NF κ B, like a corticoid steroids [111]. Trauma pain and oedema absorption are the main indications for the clinical and experimental use of this homeopathic preparation [94, 112–115].

Others studies show that Arnica montana 6cH is able to modulate the acute inflammatory process in rats, since it can increase lymphatic oedema absorption and local blood flow, as well as to promote the array of polymorphonuclear cell migration [116]. Four homeopathic remedies can be used for arthritis: causticum (6cH, 30cH) typically helpful in rheumatoid arthritis, this remedy is known for its anti-inflammatory action on the muscles, tendons, and nerves; calcarea carbonica (6cH, 30cH), this remedy has many disorders associated with calcium metabolism and is helpful in many cases of osteoarthritis; colchicum can be used for rheumatoid arthritis and gout for controlling pains in the small joints, especially the big toe, and minimal swelling; nux vomica (6cH, 30cH) in joint pains, especially in the knees [117].

These are only a few of the hundreds of homeopathic remedies that can be helpful in inflammatory conditions.

8. Topical application

The human epidermal permeabilities of different NSAIDs (salicylic acid, diethylamine salicylate, indomethacin, naproxen, diclofenac and piroxicam) from aqueous solutions is dependent on the drug's lipophilicity [118]. Topical application can be applied over the site of injury or pain area like lumbar or cervical zone and its analgesic and anti-inflammatory effects are expressed in the underlying superficial or musculoskeletal soft tissue. This modality of administration of NSAIDs acts locally and is not dependent on systemic absorption and subsequent redistribution into peripheral tissues with significantly lower systemic side effects Furthermore, it is a direct access and it allows prolonged use above all in patients who cannot use no oral medications [95, 119–120]. Of the available formulations is the epolamine salt of diclofenac that offers specific advantages for topical administration. The surfactant property of diclofenac epolamine improves hydration of the stratum corneum so it increases surface tension at the interface between the skin and the topical pharmaceutical preparation, favouring absorption [121]. Diclofenac epolamine topical patch is indicated for treatment

of acute pain of minor strains, sprains, and contusions and as a home therapy in a complex rehabilitation project in soft tissue diseases (e.g., tendonitis, epicondylitis), or rheumatologic disorders (e.g., osteoarthritis, rheumatoid arthritis), or extra-articular pathologies (e.g., fibrositis). Each adhesive patch contains 180 mg of diclofenac epolamine and inactive excipients, which enhance skin hydration and facilitate plaster adherence. Following the application of diclofenac twice daily for 5 days, were found peak plasma concentrations of 0.7–6.0 ng/mL at 10–20 hours. In the bloodstream, diclofenac has a half-life of about 12 hours and it is widely linked to albumin [122]. Its metabolism is urinary and biliary excretion of the sulfate and glucuronide conjugates. In 19 clinical trials, tolerability and efficacy of the various topical formulations of diclofenac (1.5% diclofenac sodium solution, 1.16% diclofenac diethylamine gel, 140 mg diclofenac hydroxyethylpyrrolidine patch, and 2% diclofenac lecithin organogel) have been recently revised, whereas approximately 3000 patients treated [123]. Furthermore, Diclofenac sodium 1% gel is used commonly for the relief of pain due to osteoarthritis such as the knees and those of the hands. This product contains a variety of additional ingredients in the vehicle including isopropyl alcohol, propylene glycol, and water to assist in drug penetration of the skin [124]. Topical administration is linked to local skin irritation or allergies [125].

Mg²⁺ may be one of these components because it has a significant role in energy metabolism via basic mitochondrial function, ATP transmembrane transport, muscle contraction or relaxation, membrane stability, and neuromuscular, cardiovascular, immune and hormonal functions [126–129]. Mg²⁺ depletion has been reported to decrease antioxidant capacity, increase oxidative stress, and impair intracellular calcium homeostasis that result in swelling and structural damage to muscle cells [130].

Some study shows that transdermal application may be better accepted than oral application in these patients with fibromyalgia for control of pain and inflammation because it is usually used a multitude of oral medications. Transdermal MgCl₂ solution is ideal for use in transdermal applications because it is rapidly absorbed through the skin and, therefore, can rapidly increase low or depleted levels of magnesium in the body [31, 131]. Engen et al suggest that transdermal Mg Cl₂ applied twice daily (16 sprays of MgCl₂ which equals 400 mg of magnesium) on the upper and lower limbs may be beneficial for patients with fibromyalgia [132].

9. Galenic formulations

A new galenic formulation has recently been developed. Galenic formulations with lower treatment burdens are associated with better patient compliance and persistence compared with older more burdensome modalities. Galenic formulations are characterized by low cost of the production system and the simple operative procedures; the possibility to adapt dosages and pharmaceutical forms to the patients' needs and medical prescriptions; reduction in the use of counterfeit medicines in the settings where the Galenic laboratories are located [133]. It is a therapeutic aspect evolving, so it requires others studies over the next few years.

10. Conclusion

This chapter gives an overview about the state of the art regarding the use of NSAIDs in physical and rehabilitation medicine, not only used by the classical routes of administration, but especially about the uses of these drugs through own means of this branch of medicine.

Author details

Rosa Grazia Bellomo¹, Simona Maria Carmignano², Tommaso Palermo², Lucia Cosenza², Andrea Saggini³ and Raoul Saggini^{4*}

*Address all correspondence to: saggini@unich.it

1 Department of Medical Sciences, Oral and Biotechnology, "G. d'Annunzio" University, Chieti, Italy

2 School of Specialties in PRM, "G. d'Annunzio" University, Chieti, Italy

3 Department of Biomedicine and Prevention, Institute of Anatomic Pathology, University of Rome Tor Vergata, Rome, Italy

4 Department of Medical Sciences, Oral and Biotechnology, "G. d'Annunzio" University, Chieti, Italy

References

- [1] Weiss U. Inflammation. *Nature*. 2008;**454**(7203):427. DOI: 10.1038/454427a
- [2] Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;**454**(7203): 428-435. DOI: 10.1038/nature07201
- [3] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell*. 2006;**124**(4):783-801. DOI: 10.1016/j.cell.2006.02.015
- [4] Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology*. 2006;**31**(10):2121-2131. DOI: 10.1038/sj.npp.1301029
- [5] Ding W, Stohl LL, Wagner JA, Granstein RD. Calcitonin gene-related peptide biases Langerhans cells toward Th2-type immunity. *Journal of Immunology*. 2008;**181**:6020-6026
- [6] Sauer SK, Reeh PW, Bove GM. Noxious heat-induced CGRP release from rat sciatic nerve axons in vitro. *The European Journal of Neuroscience*. 2001;**14**:1203-1208
- [7] McMahon, Bennet. Bevan's Wall and Melzack's Textbook of Pain. Elsevier Churchill Livingstone. London. 2006;49-72

- [8] Alfred IT. Metchnikoff and the phagocytosis theory. *Nature Reviews Molecular Cell Biology*. 2003;**4**:897-901. DOI: 10.1038/nrm1244
- [9] Christopher DB, Derek WG, and Charles NS. Pro-resolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity*. 2014;**40**(3):315-327. DOI: 10.1016/j.immuni.2014.02.009
- [10] Serhan CN, Savill J. Resolution of inflammation: The beginning programs the end. *Nature Immunology*. 2005;**6**(12):1191-1197. DOI: 10.1038/ni1276
- [11] Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;**444**(7121):860-867. DOI: 10.1038/nature05485
- [12] Hawkey CJ. COX-2 inhibitors. *Lancet*. 1999;**15**:307-314. DOI: 10.1016/S0140-6736(98)12154-2
- [13] Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. *The New England Journal of Medicine*. 1991;**324**(24):1716-1725. DOI: 10.1056/NEJM199106133242407
- [14] Berde C, Sundel R. COX 2 Inhibitors: A Status Report [Internet]. 1998. Available from: www.iasp-pain.org/TC98SeptOct.html
- [15] Antman EM, Bennett JS, Daugherty A. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: A scientific statement from the American Heart Association. *Circulation*. 2007;**115**(12):1634-1642. DOI: 10.1161/CIRCULATIONAHA.106.181424
- [16] World Health Organization. *Cancer Pain Relief with a Guide to Opioid Availability*. 2nd ed. Geneva; 1996. 15-16
- [17] Stöllberger C, Finsterer J. Nonsteroidal anti-inflammatory drugs in patients with cardio- or cerebrovascular disorders. *Zeitschrift für Kardiologie*. 2003;**92**(9):721-729. DOI: 10.1007/s00392-003-0964-x
- [18] Dalloz-Bourguignon A. A new therapy against pain: Mesotherapy (author's transl). *Journal Belge de Médecine Physique et de Réhabilitation* 1979;**2**:230-234
- [19] Pistor M. What is mesotherapy?. *Le Chirurgien-Dentiste de France*. 1976;**46**(288):59-60
- [20] Vecchiet L, Giamberardino MA, Saggini R. Myofascial pain syndromes: Clinical and pathophysiological aspects. *Clinical Journal of Pain*. 1991;**1**:S16-S22
- [21] Saggini R, Bellomo RG, Cancelli F, Iodice P. Treatment on myofascial pain syndromes: Local acoustic vibration vs local lidocaine. *Journal of Rehabilitation Medicine*. 2007;1650-1977
- [22] Brinks A, van Rijn RM, Willemsen SP. Corticosteroid injections for greater trochanteric pain syndrome: A randomized controlled trial in primary care. *Annals of Family Medicine*. 2011;**9**(3):226-234. DOI: 10.1370/afm.1232
- [23] Marcelli S. *Nuovo Manuale di Mesoterapia*. Ed. Milano: Ulrico Hoepli; 2013. chapt.4

- [24] Ruggeri F, Bartoletti CA, Maggiori S. Clinical results of the multicentric experimentation. *Giornale di Mesoterapia*. 1981;1:47-49
- [25] Colombo I, Cigolini M, Combi F. Clinical results of the multicentric experimentation. *Giornale di Mesoterapia*. 1981;1:50-52
- [26] Saraceni VPalieri G, De Pedis M. Clinical results of the multicentric experimentation. *Giornale di Mesoterapia*. 1981;1:53-59
- [27] Piantoni D Cotichelli E, Di Gianvito P. Clinical results of the multicentric experimentation. *Giornale di Mesoterapia*. 1981;1:60-63
- [28] Pezone A, Villa L, Martini D. Clinical results of the multicentric experimentation. *Giornale di Mesoterapia*. 1981;1:64-66
- [29] Curro F, Bearzato A. Use of the S-adenosil l-methionine ` (Same) in the treatment of degenerative arthropathies of arthrosis. *Nature*. 1981;1:99-107
- [30] Guazzetti R, Iotti E, Marinoni E. Mesotherapy with naproxin sodium in musculoskeletal diseases. *Rivista Europea Per Le Scienze Mediche E Farmacologiche*. 1988;10:539-542
- [31] Narvarte DA, Rosset-Llobet J. Safety of subcutaneous microinjections (mesotherapy) in musicians. *Medical Problems of Performing Artists*. 2011;2:79-83
- [32] Capone M, Stancati MT, Tolla V, Chiatti R, Muscolo V, Pasquale M. Observations on the administration of sodium edetate in calcified scapulohumeral periarthritis. Ionophoresis and mesotherapy: Comparison of two techniques. *Ortopedia e Traumatologia Oggi*. 1994;14:163-168
- [33] Piantoni D, Cotichellil E, Santilli W. Use of calcitonin in regional osteoporosis. *Giornale di Mesoterapia*. 1985;5:21-23
- [34] Curro F, Bearzatto A. Mesotherapy in the treatment of `post-zoster neuritis. *Giornale di Mesoterapia*. 1985;5:37-43
- [35] Curro F, Bearzatto A, Fontanini C. Mesotherapy in a general medicine department: A year of activity. *Giornale di Mesoterapia*. 1983;3:25-28
- [36] Pezone A, Santuari E, Villa ML et al. The distinct analgesicaction of calcitonin in treating painful diseases of joints with mesotherapy. *Giornale di Mesoterapia*. 1986;6:19-23
- [37] Romano M, Marccone E, Concetta Meo M, Attanasio L. Orgotein: Our experience in rheumatic pathology. *Giornale di Mesoterapia*. 1985;5:25-28
- [38] Solinas G, Solinas AL, Perra P, Solinas FL. Treatment of mechanical tendinopathies by mesotherapy with orgotein in combination with laser therapy. *Riabilitazione*. 1987;4:281-288
- [39] Garzya G, Leucci PF, Greco T, Branca L, Moschettini V. Comparative stydy of three non-steroid anti-inflammatory drugs used with mesotherapy techique in 100 geriatric patients affected by muscular -skeletal pathology. *Giornale di Mesoterapia*. 1987;7:31-44

- [40] Di Cesare A, Giombini A, Di Cesare M, Ripani M, Vulpiani MC, Saraceni VM. Comparison between the effects of trigger point mesotherapy versus acupuncture points mesotherapy in the treatment of chronic low back pain: A short term randomized controlled trial. *Complementary Therapies in Medicine*. 2011;**19**:19-26
- [41] Costantino C, Marangio E, Coruzzi G. Mesotherapy versus systemic therapy in the treatment of acute low back pain: A randomized trial. *Evidence-based Complementary and Alternative Medicine*. 2011;**2011**. pii: 317183. DOI: 10.1155/2011/317183
- [42] Saggini R, Di Stefano A, Dodaj I, Scarcello L, Bellomo RG. Pes anserine bursitis in symptomatic osteoarthritis patients: A mesotherapy treatment study. *Journal of Alternative and Complementary Medicine*. 2015;**21**(8):480-484. DOI: 10.1089/acm.2015.0007
- [43] Rawat S, Vengurlekar S, Rakesh B. Transdermal delivery by iontophoresis. *Indian Journal of Pharmaceutical Sciences*. 2008;**70**(1):5-10
- [44] Helmstädter A. The history of electrically-assisted transdermal drug delivery ("iontophoresis"). *Pharmazie*. 2001;**56**:583-587
- [45] Burton H, Sage JR. Iontophoresis. Maibach, HI, editors. In: *Percutaneous Penetration Enhancers*. Boca Raton, FL, USA: CRC Press; 1995. 351-367
- [46] Pikal MJ. The role of electroosmotic flow in transdermal iontophoresis. *Advanced Drug Delivery Reviews*. 2001;**46**(1-3):281-305
- [47] Kanikkannan N. Iontophoresis based transdermal delivery systems. *Biodrugs*. 2002;**16**:339-347
- [48] Hu QH, Liang WQ. A comparative study of electroporation and iontophoresis for percutaneous penetration of naproxen. *Pharmazie*. 2003;**58**(3):192-194
- [49] Guy RH, Hadgraft J. Rate control in transdermal drug delivery?. *International Journal of Pharmaceutics* 1992;**82**(3):DOI: 10.1016/0378-5173(92)90183-3
- [50] Fang J, et al. Passive and iontophoretic delivery of three diclofenac salts across various skin types. *Biological & Pharmaceutical Bulletin*. 2000;**23**(11):1357-1362
- [51] Hui X et al. Pharmacokinetic and local tissue disposition of sodium diclofenac following iontophoresis and systemic administration in rabbits. *Journal of Pharmaceutical Sciences*. 2001;**90**(9):1269-1276
- [52] Gay CL, et al. Iontophoretic delivery of piroxicam across the skin in vitro. *Journal of Controlled Release*. 1992;**22**(1):57-67
- [53] Curdy C, et al. Piroxicam delivery into human stratum corneum in vivo: Iontophoresis versus passive diffusion. *Journal of Controlled Release*. 2001;**76**(1-2):73-79
- [54] Tiwari SB, Udupa N. Investigation into the potential of iontophoresis facilitated delivery of ketorolac. *International Journal of Pharmaceutics*. 2003;**260**(1):93-103

- [55] Garagiola U, et al. Iontophoretic administration of piroprofen or lysine soluble aspirin in the treatment of rheumatic diseases. *Clinical Therapeutics*. 1998;**10**(5):553-558
- [56] Grossi E, et al. NSAID ionisation in the management of soft-tissue rheumatism: Role played by the drug, electrical stimulation and suggestion. *Clinical and Experimental Rheumatology*. 1986;**4**(3):265-267
- [57] Vecchini L, Grossi E. Ionization with diclofenac sodium in rheumatic disorders: A double-blind placebo-controlled trial. *Journal of International Medical Research*. 1984;**12**(6):346-350
- [58] Famaey JP, et al. Ionisation with Voltaren. A multi-centre trial. *Journal Belge de Médecine Physique et de Réhabilitation*. 1982; **5**(2):55-60
- [59] Saggini R, Zoppi M, Vecchiet F, Gatteschi L, Obletter G. Comparison of electromotive drug administration with ketorolac or with placebo in patients with pain from rheumatic disease: A double-masked study. *Clinical Therapeutics*. 1996;**18**(6):1169-1174
- [60] Baskurt F, Ozean A, Algún C. Comparison of effects of phonophoresis and iontophoresis of naproxen in the treatment of lateral epicondylitis. *Clinical Rehabilitation*. 2003;**17**:96-100
- [61] Demirtaş RN, Oner C. The treatment of lateral epicondylitis by iontophoresis of sodium salicylate and sodium diclofenac. *Clinical Rehabilitation*. 1998;**12**(1):23-29
- [62] Lerza R, Fabrizio A, Savini A, Affaitati G, Bellomo RG, Saggini R. Effects of hydroelectrophoresis (Hydrofor) on articular pain. *Dolore: Aggiornamenti Clinici*. 2009;**1-2**(S):116-117
- [63] Saggini R, D' Ettore S, Ancona E, Barassi G, Bellomo RG et al. Borsite della zampa d'oca in pazienti con gonartrosi: Studio sulla veicolazione transdermica isoforetica. conference proceedings 43° Congresso Nazionale SIMFER Ferrara 2015
- [64] Bellomo RG, Carmignano S, Ancona E, Barassi G, Saggini R. Il dolore anteriore di ginocchio in età pediatrica: dalla valutazione al trattamento sicuro ed efficace con precoce ripresa funzionale. *Giornale italiano di medicina riabilitativa*. Edizioni Minerva Medica. Volume 29 N. 2/3 Agosto-Dicembre 2015 Roma
- [65] Walters KA, Roberts MS. The structure and function of skin. Walters KA, editors. In: *Dermatological and Transdermal Formulations*. New York: Marcel Dekker; 2002. 1-40
- [66] Berardesca E, Rona C. Barriera cutanea e farmaci. In: *Tratato di Dermatologia*. Padova: Piccin; Padova 2007. pp. 1-12
- [67] Lampe MA, Burlingame AL, Whitney J, Williams ML, Brown BE, et al. Human stratum corneum lipids: Characterization and regional differences. *Journal of Lipid Research*. 1983;**24**:120-130
- [68] Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. *Advances in Lipid Research*. 1991;**24**:1-26

- [69] Kassan DG, Lynch AM, Stiller MJ. Physical enhancement of dermatologic drug delivery: Iontophoresis and phonophoresis. *Journal of the American Academy of Dermatology*. 1996;**34**:657-666
- [70] Merino G, Kalia YN, Guy RH. Ultrasound-enhanced transdermal transport. *Journal of Pharmaceutical Sciences*. 2003;**92**:1125-1137
- [71] Dinno MA, Dyson M, Young SR, et al. The significance of membrane changes in the safe and effective use of therapeutic and diagnostic ultrasound. *Ultrasound in Medicine & Biology*. 1989;**34**:1543-1552
- [72] Nyborg WL. Mechanisms. Nyborg WL, Ziskin MC, editors. In: *Biological Effects of Ultrasound*. New York, NY: Churchill Livingstone Inc; 1985:23-33
- [73] Byl NN. The use of ultrasound as an enhancer for transcutaneous drug delivery: Phonophoresis. *Physical Therapy*. 1995;**75**(6):539-553
- [74] Boyaci A. Comparison of the efficacy of ketoprofen phonophoresis, ultrasound, and short-wave diathermy in knee osteoarthritis. *Rheumatology International*. 2013;**33**:2811-2818
- [75] Tascioglu F, Kuzgun S, Armagan O, Ogutler G. Short-term effectiveness of ultrasound therapy in knee osteoarthritis. *The Journal of International Medical Research*. 2010;**38**(4):1233-1242
- [76] Luksurapan W, Boonhong J. Effects of phonophoresis of piroxicam and ultrasound on symptomatic knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation*. 2013;**94**:250-255
- [77] Ay S, Doğan SK, Evcik D, Başer OC. Comparison the efficacy of phonophoresis and ultrasound therapy in myofascial pain syndrome. *Rheumatology International*. 2011;**31**:1203-1208. DOI: 10.1007/s00296-010-1419-0
- [78] Shin SM, Choi JK. Effect of indomethacin phonophoresis on the relief of temporomandibular joint pain. *Cranio*. 1997;**15**:345-348
- [79] Gaofeng Y. Natural products and anti-inflammatory activity. *Asia Pacific Journal of Clinical Nutrition*. 2006;**15** (2):143-152
- [80] Weiss RF. In: *Weiss's Herbal Medicine*. Stoccarda: Classic Edition Thieme; Stoccarda 2001
- [81] Golberg G. *Plants: Diet and Health. The Report of a British Nutrition Foundation Task Force*. British Nutrition Foundation, Blackwell Publishing. 2003; 1-26. DOI: 10.1002/9780470774465
- [82] Satoskar RR, Shah SJ, Shenoy SG Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. *International Journal of Clinical Pharmacology, Therapy, and Toxicology*. 1986;**24**(12):651-654
- [83] Ammon HP, Safayhi H, Mack T, Sabieraj J. Mechanism of antiinflammatory actions of curcumin and boswellic acids. *Journal of Ethnopharmacology*. 1993;**38**:113-119

- [84] Jian YT, Wang JD, Mai GF, Zhang YL, Lai ZS. Curcumin regulates cyclooxygenase-2 activity in trinitrobenzene sulfonic acid-induced colitis. *Journal of Fourth Military Medical University*. 2005;**26**:521-524
- [85] Skrzypczak-Jankun E, McCabe NP, Selman SH, Jankun J. Curcumin inhibits lipoxigenase by binding to its central cavity: Theoretical and X-ray evidence. *International Journal of Molecular Medicine*. 2000;**6**:521-526
- [86] Joe B, et al. Presence of an acidic glycoprotein in the serum of arthritic rats: Modulation by capsaicin and curcumin. *Molecular and Cellular Biochemistry*. 1997;**169**(1-2):125-134
- [87] Onodera S, Kaneda K, Mizue Y, Koyama Y, Fujinaga M, Nishihira J. Macrophage migration inhibitory factor up-regulates expression of matrix metalloproteinases in synovial fibroblasts of rheumatoid arthritis. *The Journal of Biological Chemistry*. 2000;**275**:444-450
- [88] Lev-Ari S, Strier L, Kazanov D, Elkayam O, Lichtenberg D. Curcumin synergistically potentiates the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis synovial adherent cells. *Rheumatology (Oxford)*. 2006 Feb;**45**(2):171-7. Epub 2005 Oct 25
- [89] Halpern GM. Anti-inflammatory effects of a stabilized lipid extract of *Perna canaliculus* (Lyprinol). *Allergie und Immunologie*. 2000;**32**:272-278
- [90] Murphy KJ, Kiely M, Galvin K, Morrissey PA, Mann NJ, Sinclair AJ. New Zealand green lipped mussel (NZGLM) oil can reduce pro-inflammatory eicosanoids and cytokines and oxidation markers in vivo. *Proceeding of the Nutrition Society of Australia*. 2002;**26**:S289
- [91] Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a treatment for osteoarthritis: A review of clinical studies. *Evidence-based Complementary and Alternative Medicine*. 2004;**1**:251-257
- [92] Foster S, Tyler VE. *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies*. Binghamton, NY: Haworth Herbal; 1999;39-41
- [93] Totonchi A, Guyuron B. A randomized, controlled comparison between arnica and steroids in the management of postrhinoplasty ecchymosis and edema. *Plastic and Reconstructive Surgery*. 2007;**120**:271-274
- [94] Karow JH, Abt HP, Frohling M, et al. Efficacy of arnica montana D4 for healing of wounds after Hallux valgus surgery compared to diclofenac. *Journal of Alternative and Complementary Medicine*. 2008;**14**:17-25
- [95] Moore RA, Tramer MR, Carroll D, et al. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ*. 1998;**316**:333-338
- [96] Lyss G, Schmidt TJ, Merfort I, Pahl HL. Helenalin, an anti-inflammatory sesquiterpene lactone from Arnica, selectively inhibits transcription factor NF-kappaB. *Biological Chemistry*. 1997 Sep;**378**(9):951-61

- [97] Schmidt C. A double-blind, placebo-controlled trial: Arnica montana applied topically to Subcutaneous mechanical injuries. *Journal of the American Institute of Homeopathy*. 1996;**89**:186
- [98] Bellavite P. Historical background. *Immunology and Homeopathy*. 2005;**2**(4)441-452
- [99] Frase W. La eficacia de las diluiciones homeopaticas en forma de acordes de potencias. *Med Biol—Int J Biomed Res Ther*. 1999;**12**(2):59-61
- [100] Belon P, Cumps J, Ennis M, et al. Inhibition of human basophil degranulation by successive histamine dilutions: Results of a European multi-centre trial. *Inflammation Research*. 1999;**48**(suppl. 1):S17
- [101] Belon P, Sainte-Laudy J. Inhibition of human basophil activation by high dilutions of histamine. *Agents and Actions*. 1993;**38**:C245-C247
- [102] Carvalho AC, Bonamin LV. Efeito da administração de Arnica montana (tintura-mãe e preparações dinamizadas 6CH) na atividade de diferentes agentes flogísticos em ratos. *Pesq Hom*. 2001;**16**:31-43
- [103] Poitevin B, Aubin M, Royer JF. Belladonna and Ferrum phosphoricum effect in chemiluminescence of polynuclear neutrophils. *Ann Hom Farina*. 1983;**3**:5-12
- [104] Winterberg H. Belladonna—Childhood diseases with particular reference to bronchitic inflammations. *Biological Theroy of Journal Nature Medicine*. 1986;**3**(4):79-81
- [105] Galvão GG. A symptomatic totality's study of Stramonium, Belladonna and Hyoscyamus. *Anais do XXI Congresso Brasileiro de Homeopatia*. 1992;**3**:35
- [106] Bauer R. Echinacea drugs—effects and active ingredients. *Zeitschrift fur Arztliche Fortbildung*. 1996;**90**:111-115
- [107] Wildfeuer A, Mayerhofer D. The effects of plant preparations on cellular functions in body defense. *Arzeimttelforschung*. 1994;**44**:361-366
- [108] Hu C, Kitts DD. Studies on the antioxidant activity of Echinacea root extract. *Journal of Agricultural and Food Chemistry*. 2000;**48**:1466-1472
- [109] Carvalho AC. Efeitos da administração de Arnica montana (tintura-mãe e UHD) na atividade de diferentes agentes flogísticos em ratos. In: Master of Science Dissertation. Instituto de Ciências da Saúde, Universidade Paulista—UNIP; Brasília. 2000
- [110] Macêdo SB, Ferreira LR, Perazzo FF, Tavares Carvalho JC. Anti-inflammatory activity of Arnica montana 6CH: Preclinical study in animals. *Homeopathy*. 2004;**93**:84-87
- [111] Klaas CA, Wagner G, Laufer S et al. Studies on the anti-inflammatory activity of phytopharmaceuticals prepared from Arnica flowers. *Planta Medica*. 2002;**68**:385-391
- [112] Bellavite P, Ortolani R, Conforti A. Immunology and homeopathy. Experimental studies on animal models. *Evidence-based Complementary and Alternative Medicine*. 2006;**3**:171-186

- [113] Bellavite P, Conforti A, Pontarollo F, Ortolani R. Immunology and homeopathy. Cells of the immune system and inflammation. Evidence-Based Complementary and Alternative Medicine. 2006;**3**:13-24
- [114] Conforti A, Bellavite P, Bertani S, Chiarotti F, Raschetti R. Rat models of acute inflammation: a randomized controlled study on the effects of homeopathic remedies. BMC Complementary and Alternative Medicine. 2007;**7**:1
- [115] Palombo EA. Traditional medicinal plant extracts and natural products with activity against oral bacteria: Potential application in the prevention and treatment of oral diseases. Evidence-based Complementary and Alternative Medicine 2011;**2011**:680354
- [116] Bonamin LV. Arnica montana and behavior of connective tissue. In: Signals and Images: Contributions and Contradictions of High Dilution Research. Springer; 2008. 113-125
- [117] Fisher P, Scot DL. A randomized controlled trial of homeopathy in rheumatoid arthritis. Rheumatology. Oxford 2001;**40**:1052-1055
- [118] Ballerini R, Casini A, Chinol M, Mannucci C, Giaccai L, Salvi M. Study on the absorption of ketoprofen topically administered in man: Comparison between tissue and plasma levels. International Journal of Clinical Pharmacology Research. 1986;**6**(1):69-72
- [119] Dreiser RL. Topical antirheumatic drug therapy: Current practice and future trends. European Journal of Rheumatology and Inflammation. 1994;**14**(4):3-8. 27
- [120] Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: Current and future prospects. Drug Delivery. 2006;**13**(3):175-187
- [121] Fini A, Fazio G, Rapaport I. Diclofenac/N-(2-hydroxyethyl) pyrrolidine: A new salt for an old drug. Drugs under Experimental and Clinical Research. 1993;**19**(3):81-88
- [122] Rusca A, Mautone G, Sun S, Magelli M, Johnson F. Comparison of plasma pharmacokinetics of FLECTOR® Patch (diclofenac epolaminetopical patch) and oral Voltaren® (diclofenac sodium enteric coated tablets) in healthy volunteers. The Journal of Pain. 2008;**9**(4 Suppl 1):45
- [123] Zacher J, Altman RA, Bellamy N, et al. Topical diclofenac and its role in pain and inflammation: An evidence-based review. Current Medical Research and Opinion. 2008;**24**:925-950
- [124] Barthel HR, Haselwood D, Longley S 3rd, Gold MS, Altman RD. Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis. Seminars in Arthritis and Rheumatism. 2009 Dec;**39**(3):203-212
- [125] Gallacchi G, Mautone G, Lualdi P. Painful inflammatory conditions: Topical treatment with diclofenac hydroxyethylpyrrolidine (Flector Gel 1%). Clinical Trials Journal. 1990;**27**(1):58-64
- [126] Larkson PM, Haymes EM. Exercise and mineral status of athletes: Calcium, magnesium, phosphorus, and iron. Medicine and Science in Sports and Exercise. 1995;**27**:831-843

- [127] Dickens BF, Weglicki WB, Li YS, Mak IT. Magnesium deficiency in vitro enhances free radical induced intracellular oxidative and cytotoxicity in endothelial cells. *FEBS Letters*. 1992;**311**:187-191
- [128] Dominguez LJ, Barbagallo M, Lauretani F, Bandinelli S, et al. Magnesium and muscle performance in older persons: The InCHIANTI study. *The American Journal of Clinical Nutrition*. 2006;**84**:419-426
- [129] Finstad EW, Newhouse IJ, Lukaski HC, McAuliffe JE, Stewart CR. The effects of magnesium supplementation on exercise performance. *Medicine and Science in Sports and Exercise*. 2001;**33**:493-498
- [130] Volpe SL. Magnesium in disease prevention and overall health. *Advances in Nutrition*. 2013;**4**:378-383
- [131] Watkins K, Josling PD. A Pilot Study to Determine the Impact of Transdermal Magnesium Treatment on Serum Levels and Whole Body CaMg Ratios. Spring; 2010
- [132] Engen DJ, McAllister SJ, Whipple MO. Effects of transdermal magnesium chloride on quality of life for patients with fibromyalgia: A feasibility study. *Journal of Integrative Medicine*. 2015;**13**(5):306-313
- [133] Barata F, Germano A, Di Lascio G. Establishment of galenic laboratories in developing countries to produce high quality medicines: results of Aid Progress Pharmacist Agreement (A.P.P.A.®) Project. *Croatian Medical Journal*. 2014;**55**(6):662-668