

A novel boswellic acids delivery form (Casperome®) in the management of musculoskeletal disorders: a review

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Abstract. – Standard pharmacological treatment of musculoskeletal conditions is often associated with relevant side effects. Botanical preparations endowed with a good tolerability profile, therefore, could have a role in the management of these disorders. Among different natural products, *Boswellia serrata* extracts have long been used for the treatment of musculoskeletal disorders, given their marked anti-inflammatory activity and their ability to promote tissue regeneration. However, standard preparations of *Boswellia serrata* show overall modest pharmacokinetic properties, a limitation which may ultimately lead to reduced efficacy.

In an effort to improve the pharmacokinetic properties, Casperome®, a lecithin-based formulation of *Boswellia serrata* extract representing the whole natural bouquet, has been developed. This formulation was effective in the treatment of Achilles tendonitis, epicondylitis, radiculopathies, ankle sprains and sport injuries as shown in several clinical studies, the majority of which with a randomized design and all evaluating a number of well-recognized parameters of efficacy for the therapy of musculoskeletal disorder. All studies were consistent in showing a prompt decrease of pain and improvement of functionality of the affected area after supplementation with Casperome®, without any relevant adverse effect. Remarkably, these symptomatic improvements were paralleled by reduced plasmatic levels of inflammatory markers and by a diminished need for rescue analgesics.

On these bases, Casperome® may have a role in the treatment of musculoskeletal disorders. Clinical studies in other similar conditions (e.g., osteoarthritis) appear warranted to further investigate the efficacy of this botanical product in more specific settings.

Key Words:

Boswellia, Casperome, Musculoskeletal disorders.

Introduction

Musculoskeletal conditions represent the most common cause of chronic disability worldwide, and are associated with a major burden to the healthcare system¹. They include, but are not limited to, osteoarthritis, inflammatory arthritis, and musculoskeletal injuries, including sports injuries, gout and metabolic bone disease¹. Estimates of the global burden of these musculoskeletal conditions show a 25% increase over the past decade¹.

Symptomatic treatments for musculoskeletal disease are mainly aimed at reducing pain associated with these conditions and restore full functionality of the affected tissues. To this end, nonpharmacological treatments (e.g., massage, heat, ice, physiotherapy) may be useful in the short term. Pharmacological treatment is based on analgesic and/or anti-inflammatory agents such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs); if no response occurs, then combination treatment or opioid derivatives may be useful. However, pharmacological therapy, especially when administered via a systemic route, can be associated with a number of adverse effects, including gastrointestinal disturbance, hemorrhage, constipation and disorientation^{1,2}.

Without neglecting the important contribution represented by synthetic anti-inflammatory drugs, botanical extracts are also used extensively for the management of musculoskeletal conditions in the effort to limit the risk of adverse events while retaining clinical efficacy^{1,3}. Noteworthy, these supplementations may have a beneficial effect also on the course of the disease^{3,4}.

In particular, *Boswellia serrata* gum resin extract (BSE) containing boswellic acids (BAs) as the main bioactive principles, has been shown effective in the management of musculoskeletal pain and inflammation⁴⁻⁷. A lecithin-based delivery system of BAs (Casperome®, Indena S.p.A., Italy) has been recently developed to enhance the pharmacokinetic properties of these compounds⁸.

We discuss here available evidences on the use of BAs in musculoskeletal conditions, focusing on the recent clinical studies on Casperome®.

Boswellic Acids in Musculoskeletal Conditions: an Overview

Boswellic acids are the main bioactive constituents of frankincense, a traditional remedy used in Indian, Chinese, and African folk medicine endowed with anti-arthritic, astringent, stimulant, expectorant and antiseptic properties⁹. The most important frankincense sources are *Boswellia serrata* in Northwestern India and *Boswellia carterii* in Africa.

Several experimental and clinical data show the potential of BSE for the treatment of a various inflammatory diseases such as bowel diseases and asthma^{5,10-16}. Moreover, a number of studies do support the rationale for the use of BSE in musculoskeletal disorders, thanks to the inhibition of the molecular mechanisms underlying these conditions³.

Experimental Studies

Boswellia preparation reduced the synthesis and the activation of several inflammation mediators (MMP-9 and MMP-13, cyclooxygenase-2, nitric oxide, prostaglandin E2), thus slowing down collagen and cartilage dissolution¹⁷⁻¹⁹. Decreased inflammation, slowed cartilage deterioration and increased synthesis of structural proteins were also reported in other *in vitro* studies on a poly-herbal formulation which included BSE^{4,19}.

These effects were observed also in animal models. In rats, BSE suppressed pro-inflammatory mediators and improved the antioxidant status, as reflected by lactoperoxidase, myeloperoxidase, catalase, superoxide dismutase (SOD), glutathione (GSH), nitric oxide (NO) levels²⁰. Together with *Withania somnifera*, *Zingiber officinale* and *Curcuma longa*, BSE relieved inflammation and arthritis, and also reduced the synthesis of TNF- α and NO²¹.

Clinical Studies

According to a Cochrane systematic review, BSE presents some benefits in the treatment of osteoarthritis, coupled with a low burden of side effects, in four clinical, placebo-controlled studies⁶. In particular, BSE was superior vs. placebo in reducing pain and increasing functionality.

Indeed, in two well-conducted, double-blind, randomized, placebo-controlled studies in patients with knee osteoarthritis, BSE induced pain relief and increased functionality as early as a few days since treatment initiation^{17,22}. In a registry study, the supplementation with *Boswellia* preparation showed benefits in the treatment of knee osteoarthritis when added to the standard management, ameliorating both symptoms and functional status²³. It also accelerated functional recovery and decreased pain and inflammation in hand arthritis induced by work-related overstraining²⁴. A combination of *Curcuma longa* and BSE was superior over celecoxib – in terms of efficacy and safety – in patients with knee osteoarthritis²⁵. However, these findings were challenged by the non-positive results of another double-blind study in rheumatoid arthritis patients²⁶.

Casperome® in the Treatment of Musculoskeletal Conditions: Rationale and Clinical Evidence

Pharmacokinetic studies in both animal models and humans have shown that, after oral administration of BSE (with a dosage as high as 3000 mg/day), plasma concentrations of BAs remain modest, potentially below the pharmacologically active concentrations^{5,8,27}. This limitation in pharmacokinetic profile has somehow limited the use of BSE in clinical practice and its pharmaceutical development.

Of note, the modest oral adsorption of BAs is not surprising. Indeed, these compounds are poorly soluble in water, suggesting a tendency to self-aggregation. This hypothesis is supported by the increased absorption when BSE are administered together with food, and therefore self-aggregates may be dissolved biliary salts²⁸.

These observations provided a rationale for the development of a lecithin-based formulation of BAs (Casperome®). This formulation improved absorption of BAs and enhanced tissue accumulation as showed in an animal study, which demonstrated plasma concentrations of BAs well-above the lower threshold of anti-inflammatory activity²⁹. In a subsequent randomized crossover study, 12 healthy volunteers alternatively

received Casperome[®] or non-formulated BSE⁸. Overall, a significantly higher (both in terms of weight-to-weight and molar comparison) and quicker absorption of BAs was observed with the administration of Casperome[®].

On these bases, Casperome[®] has been used in several clinical studies of different inflammatory-based conditions, including musculoskeletal disorders such as tendinopathies, radiculopathies, ankle sprains and sport-related injuries^{2,11,14,16,30-33}. Clinical evidence on the efficacy and safety of Casperome[®] in these conditions is described below.

Tendinopathies

Achilles tendonitis and epicondylitis are tendinopathies commonly encountered in daily practice. In a randomized trial, with an open design, 60 patients (30 with Achilles tendonitis and 30 with epicondylitis) were assigned to physical therapy only (n=15 among subjects with Achilles tendonitis and n=15 among those with epicondylitis) or physical therapy plus Casperome[®] 250 mg based supplement b.i.d (Tendhyal[®]; n=15 in each subgroup)³⁰. Overall, 30 days since the initiation of the study, assessment by visual-analogical scale showed a lower pain score with Casperome[®] plus physical therapy, as compared with physical therapy only both in subjects with Achilles tendonitis (1.60±0.34 vs. 3.40±0.45; $p<0.05$) and in those with epicondylitis (1.33±0.39 vs. 2.80±0.40; $p<0.05$). Noteworthy, improved pain reduction with Casperome[®] was already evident at day 7 in subjects with epicondylitis. Patients assigned to Casperome[®] group also presented improved function at 15 and 30 days, compared with those on physical therapy only. The proportion of subjects needing paracetamol was constantly lower with Casperome[®].

Radiculopathies

In a prospective, randomized, open-label study on patients with cervical and lumbar radiculopathy due to nerve root compression, Casperome[®] 250 mg in combination with (R+) thioctic acid (Destior Bridge[®]) was compared with (R+) thioctic acid only, a neuroprotective and antioxidant agent used for the treatment of these conditions³¹. In more details, 90 patients were randomly assigned to three treatment groups: group DB15+30 received (R+) thioctic acid plus Casperome[®]-based supplement for 15 days followed by (R+) thioctic acid only for 30 days; group DB10+20 received (R+) thioctic acid plus Casperome[®]-based supplement for 10

days followed by (R+) thioctic acid only for 20 days; group D received (R+) thioctic acid only for 30 days.

Overall, group DB15+30, with a longer exposure to Casperome[®], achieved better results than group DB10+20 and D in terms of pain control and reduction of functional impairment at 10 and 30 days since treatment initiation.

During another randomized clinical study, Casperome[®] plus (R+) thioctic acid (the former for 10 days, followed by 20 days of thioctic acid only) were compared with (R+) thioctic acid only in patients with cervical or lumbar radiculopathy of moderate severity and neuropathic pain (n=30 for each group)³². Enrolling criteria included moderate severity, recent onset and neuropathic pain. Overall, both treatments determined a significant improvement in pain severity and functional status at 30 days; however, the improvement vs. baseline was already evident at day 10 in subjects assigned to Casperome[®] group.

Ankle Sprains

Ankle sprains represent a reliable model of soft tissue injury. In a recent study, patients with grade II ankle sprains were advised to either follow a standard management (n=37) or to follow standard management plus Casperome[®] 250 mg/day (n=35)². Casperome[®] supplementation significantly reduced both spontaneous and on movement pain already at day 3, as compared with baseline (spontaneous pain, evaluated by VAS: 73.3±5.4 at baseline and 42.2±3.0 at day 3, $p<0.05$; on movement pain, 87.4±5.2 and 31.2±2, respectively, $p<0.05$). This improvement was still evident at day 7. On the other hand, patients on standard management only did not show any improvement in pain. Noteworthy, 78% of patients on Casperome[®] had a complete resolution of injury at day 7, vs. 38% of those on standard management only. Casperome[®] added to standard management was also more beneficial on other clinical signs and symptoms of inflammation than standard management only. Furthermore, Casperome[®] supplementation allowed measurable plasma level of boswellic acids even with a once-daily administration. No side effects associated with Casperome[®] were reported.

Sport Injury

In a clinical research on elite young rugby players (mean age, 18 years) with acute knee pain and inflammation due to sport trauma,

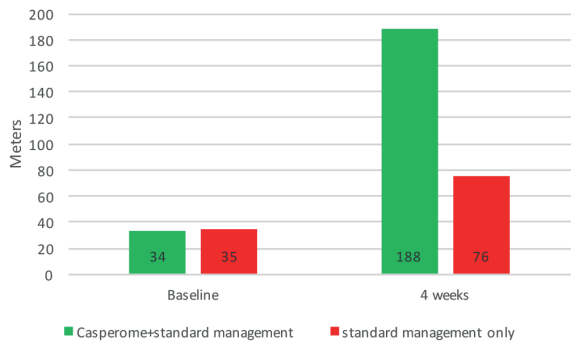


Figure 1. Pain-free walking distance, at baseline and after a 4-week follow-up, in elite young rugby players who received Casperome®+standard management (n=25) or standard management only (n=27) for the treatment of a sport-related injury. $p < 0.05$ for Casperome®+standard management vs. standard management only at week 4.

Casperome® 250 mg/day plus standard management (n=25) was compared with standard management only (n=27) in relieving musculoskeletal pain and inflammation³³. After a 4-week follow-up, only 6 subjects on Casperome® plus standard management showed local pain, vs. 25 at baseline (-20.4%, $p < 0.05$). Corresponding figures for rugby players with joint effusion and those with hematomas were -35.3% and -28.2%, respectively ($p < 0.05$ for all comparisons). Subjects in the Casperome® group also showed increased pain-free walking distance at the treadmill test (baseline: 34.8±8.2 meters; 4 weeks: 188±12.7; $p < 0.05$) [Figure 1], and had lower concentrations of biomarkers of inflammation such as CRP and of cartilage degradation such as COMP. On the other hand, no improvement vs. baseline was observed for standard management only in any parameter. Noteworthy, players on Casperome® showed a more evident decrease in high temperature areas of the injured limb compared with those on standard management only (-66% vs. -44%; $p < 0.05$). The maximum temperature area associated with injury decreased in only 4 days of supplementation with Casperome® supporting a faster relief with this botanical preparation. Moreover, in the Casperome® group the reduction in the need for other analgesic treatments was significantly greater than in the standard-management group: at 4 weeks, only 2 out of 25 subjects on Casperome® needed NSAIDs vs. 9/27 in the control group ($p < 0.05$; Figure 2). No side effects were reported.

Discussion

Musculoskeletal disorders are frequently encountered in clinical practice and are associated with important disability and major healthcare burden. Of note, standard pharmacological treatment of these conditions is often associated with relevant side effects, which may limit their use.

Botanical preparations have therefore a major potential role in the management of musculoskeletal disorders. However, it is of utmost importance that the efficacy and safety of these remedies are sustained by well-designed clinical studies, conducted with standardized and reproducible preparations meeting high-quality requirements.

BSEs have long been used for the treatment of musculoskeletal disorders, given their marked anti-inflammatory activity and their ability to promote tissue regeneration. However, standard preparations of BAs show overall modest pharmacokinetic properties, a limitation which may ultimately lead to reduced efficacy.

In an effort to improve the pharmacokinetic properties of BAs, Casperome® a lecithin-based formulation of BSA representing the whole natural bouquet of *Boswellia*, has been developed. This formulation was effective in a number of clinical studies on different conditions based on inflammation, such as asthma, ulcerative colitis and inflammatory bowel syndrome^{11,14,16}. Moreover, Casperome® was effective in the treatment of Achilles tendonitis, epicondylitis, radiculopathies, ankle sprains and sport injuries alone or in combinations as shown by several trials, the ma-

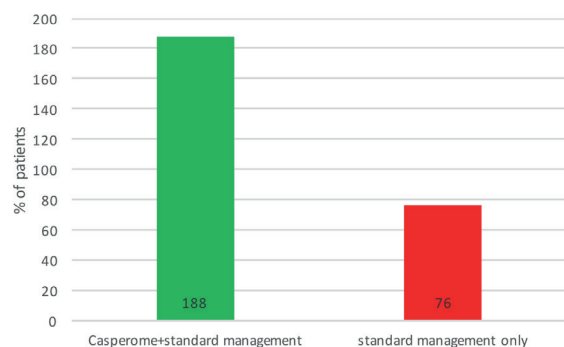


Figure 2. Need of analgesic therapy, after a 4-week follow-up, in elite young rugby players who received Casperome®+standard management (n=25) or standard management only (n=27) for the treatment of a sport-related injury. $p < 0.05$ for Casperome®+standard management vs. standard management only.

majority of which with a randomized design and all evaluating a number of well-recognized parameters of efficacy for the therapy of musculoskeletal disorder^{2,30-33}. All clinical studies were consistent in showing a prompt decrease of pain and improvement of functionality of the affected area after Casperome[®] supplementation, without any relevant adverse effect. Remarkably, these symptomatic improvements were paralleled by reduced plasmatic levels of inflammatory markers and by a diminished need for rescue analgesics.

Conclusions

On these bases, Casperome[®], under proper medical control and within an integrated management, does have a role in the treatment of musculoskeletal disorders. Studies in other similar conditions (e.g., osteoarthritis) appear warranted to further investigate and extend the efficacy of this phytosome to more specific settings.

Conflict of interest

AR, PA, FF and ST are employees of Indena S.p.A. LG is a consultant of Indena S.p.A. RE declares no conflict of interest.

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