European Review for Medical and Pharmacological Sciences 2016; 20: 4156-4161

A novel lecithin based delivery form of Boswellic acids (Casperome®) for the management of osteo-muscular pain: a registry study in young rugby players

F. FRANCESCHI[1], S. TOGNI[1], G. BELCARO[2], M. DUGALL[2], R. LUZZI[2], A. LEDDA[2], L. PELLEGRINI[2], R. EGGENHOFFNER[3], L. GIACOMELLI[3]

[1]Indena SpA, Milan, Italy
[2]Department SMO Biotech, Irvine[3] Labs, Circulation Sciences, Chiti-Pescara University, Italy
[3]Department of Surgical Sciences and Integrated Diagnostics, School of Medicine, Genova University, Genoa, Italy

Abstract. – OBJECTIVE: Several experimental studies and clinical trials support the potential of *Boswellia serrata* extracts (BSE) for the treatment of various inflammatory diseases. The aim of this registry study was to assess the safety and the efficacy of a novel lecithin-based delivery form of *Boswellia serrata* extract (Casperome®) in the supportive management of osteo-muscular pain.

PATIENTS AND METHODS: 52 healthy young rugby players with acute knee pain and inflammation were recruited. Informed participants freely decided to follow either a standard management (SM) to control joint pain (control group = 27) or SM associated with oral daily supplementation with Casperome® (supplement group =25). Parameters associated with osteo-muscular pain and inflammation, and measurements of joint health and functions were assessed at the inclusion and after a 4-week supplementation.

RESULTS: A significant beneficial effect of Casperome® vs SM alone was observed for all the parameters evaluated, namely: local pain on effort; pain-free walking distance (treadmill test); minimal joint effusion; structural damage (joint, tendons, muscles) and intramuscular hematomas; thermal imaging of the anterior knee; Visual Analog Scale for Pain (VAS Pain); need for concomitant drugs and medical attention; measurement of inflammatory biomarkers.

CONCLUSIONS: Our registry study suggests that Casperome® supplementation could represent an effective and safe, integrated approach for the treatment of osteo-muscular pain and inflammation.

Key Words:
Boswellia serrata, Phytosome®, Casperome®, Knee pain, Supplements, Osteo-muscular pain.

Introduction

Boswellic acids are the main bioactive constituents of frankincense, a traditional remedy of the Indian, Chinese, and African folk medicine with antiarthritic, astringent, stimulant, expectorant and antiseptic properties[1]. Frankincense is the common name of the gum-resin from various *Boswellia* species. The most important frankincense-producing species are *Boswellia serrata* in Northwestern India and *Boswellia carterii* in Africa (Northern Somalia, Sudan, Eritrea, and Ethiopia). A bulk of experimental data from *in vitro* and *in vivo* studies, and pilot clinical trials support the potential of *Boswellia serrata* gum resin extract (BSE) for the treatment of a various inflammatory diseases such as bowel disease, rheumatoid arthritis, osteoarthritis and asthma[2-8]. Moreover, in 2002 the European Medicines Agency classified BSE as an 'orphan drug' for the treatment of peritumoral brain oedema[2]. Noteworthy, a recent Cochrane review investigating the effects of herbal therapies in osteoarthritis (OA), reported a high-quality evidence that *Boswellia serrata* slightly improved pain and function in patients affected with osteoarthritis[9]. Compared with the non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, the most frequent therapeutic approaches for chronic and acute inflammatory diseases such as osteo-muscular pain, BSE is associated with improved tolerability[10]. Historically, the pharmacological effects of BSE have been mainly attributed to boswellic acids, especially 11-keto-β-boswellic acid (KBA) and

Corresponding Author: Gianni Belcaro, MD; e-mail: cardres@abol.it

acetyl-11-keto-b-boswellic acid (AKBA), which were described as selective 5-lipoxygenase inhibitors[11]. However, more modern publications have questioned both the correctness of this purported biological target[12] and the cellular availability of KBA and AKBA[13], thus suggesting that previous literature has been barking up the wrong tree with the wrong dog.

Furthermore, various pharmacokinetic studies have revealed low systemic absorption of boswellic acids, particularly AKBA and KBA, in animals and human[14]. In order to improve the bioavailability of BSE and its biological effect, a lecithin-based delivery form of standardized BSE (Casperome®) has been created encompassing the full bouquet of naturally present boswellic acids[15,16] and without artificially enriching (to no purpose, as the recent medical literature suggests) the extract in AKBA and KBA.

Osteo-muscular pain in elite athletes is the most prevalent complaint in the sport medicine practice. Knee pain is a broad clinical entity including over-use issues as well as traumatic injuries[17]. Studies[17,18] have reported the high risk of knee injuries especially in athletes engaged in high impact and ball sports such as football (soccer), basketball and rugby.

Given the efficacy of BSE in the treatment of OA[19-21], this study aimed at evaluating for the first time the efficacy of a novel delivery form of *Boswellia serrata* extract (Casperome®) on parameters of osteo-muscular pain and measurements of joint health and functions, in young rugby players suffering from osteo-muscular and knee pains.

Patients and Methods

Subjects and Procedures

This was an open label, registry, supplement study (see[20,21] for a complete description of such studies), conducted in 52 male rugby players with knee pain without OA or other bone, joint or muscular lesions (as documented by magnetic resonance, x-ray or ultrasound), for 4 weeks.

Potential subjects were excluded from the study if they met the following criteria:

– concomitant diseases or risk conditions requiring drug treatment
– body mass index (BMI) >25
– severe metabolic disorders
– surgery or arthroscopy within three months before inclusion
– oncological diseases
– bone/joint deformation
– osteoporosis or conditions making the patient unable to walk

All participants gave written informed consent before enrolment in this study. All procedures received local Ethics Committee approval, in accordance with the latest version of the Declaration of Helsinki.

Informed participants (n=52) freely decided to follow either a standard management (SM) to control joint pain (control group = 27) or SM associated with oral daily supplementation (supplement group = 25). Standard management (SM) of knee pain includes: rest; rehabilitative and supportive measures; adjunctive drug therapy, namely analgesics (such as acetaminophen) and anti-inflammatory agents with analgesic properties (such as NSAIDs).

Supplementation consisted of 500 mg/day of the new standardized BSE, Casperome® (2 tablets of 250 mg, in single administration) for 5 days, followed by 250 mg/day of Casperome® (1 tablet, in single administration) for 23 days. The dosage scheme was designed based on the pharmacokinetics features of Casperome®[22], supporting a once a day administration.

The following parameters were evaluated before and at the end of the observational period: 1) number of subjects with local pain on effort; 2) pain-free walking distance (treadmill test); 3) number of subjects with minimal joint effusion by high-resolution ultrasound; 4) number of subjects with structural damage (joint, tendons, muscles) and intramuscular hematomas by using high-resolution ultrasound of the painful areas; 5) side-to-side temperature difference of the injured anterior knee measured by thermal imaging (FLIR 440, Sweden)[23]; 6) Visual Analog Scale for Pain (VAS Pain)[24], ranging from 0 to 5; 7) number of subjects using concomitant drugs and medical attention during the 4 week study. Subjects were trained to perform the treadmill test in two tutorials and performances were evaluated using the treadmill at a speed of 3 km/hour with an inclination of 10 percent. The total distance that could be covered without significant pain (inducing the subject to slow down or to stop) was recorded at the inclusion and the end of the study. Basic blood tests and physiological parameters were also evaluated before and after the observational period.

Treatment Formulations

Casperome® (Indena, Milan, Italy) is a delivery form of a highly standardized *Boswellia serrata*

Table I. Details of subjects enrolled in the study

	Standard Management	Standard Management + Casperome®
Subjects	27	25
Age, years (mean ± SD)	18.1±3.3	18.3±4.3

SD: standard deviation.

extract and soy lecithin in a 1:1 ratio, with about half part of microcrystalline cellulose being also added to improve the physical state and to standardize the product to a content of triterpenoid acids by HPLC of at least 25%.

Measurement of Inflammatory Biomarkers

Plasma levels of the cartilage oligomeric matrix protein (COMP) and C-reactive protein (CRP) were measured according to Bedi et al[25], as markers of cartilage damage and inflammation respectively. Circulating biomarkers of cartilage damage and inflammation were evaluated at inclusion and the end of the registry study.

Statistical Analysis

Data were analyzed by descriptive statistics. Numerical data comparison between groups was performed by using unpaired two-sample Student's *t*-test or Mann-Whitney U test, as appropriate. Categorical data differences between groups were evaluated by chi-squared test. *p*-values less than 0.05 were considered significant. According to previous studies on comparable groups, at least 20 subjects were considered adequate to define a difference in target outcomes at 4 weeks.

Results

Details of the two groups are shown in Table I. Neither safety and tolerability issues nor clinically relevant variations in the blood and physiological parameters were observed at inclusion and at the 12-week re-evaluation (data not shown). As summarized in Table II, we observed a significant beneficial effect of Casperome® supplementation, compared with only standard management, in all the tested parameters. High-resolution ultrasound of the painful areas focusing on structural integrity, occurrence of minor intramuscular hematomas and alterations (Table II, parameter 4) was negative for major structural damages (joint, tendons, muscles). However, at inclusion the ultrasound scans observed minor intramuscular hematomas (<0.5 cm) in 12 and 13 subjects using SM + Casperome® supplement and SM only, respectively. At 4 weeks, hematomas disappeared in most subjects using the supplement, with 4 remaining subjects showing lesions (vs 8 subjects using the SM). In addition to a significant decrease of the side-to-side temperature differences (Table II, parameter 5), thermographic images of the anterior knee showed the evolution of the higher temperature areas: the initial area being 100%, the mean decrease in hyperthermic area was of 66±4.2% in the SM+Casperome® group compared to 45.4±4.5% in controls group ($p<0.05$) (Figure 1A). The decrease in hyperthermic areas was also very fast in the Casperome®-supplemented group. In fact, the maximum temperature area (white, white-red) associated to the painful spots decreased in only 4 days of supplementation with Casperome® (Figure 1B). The need for concomitant drugs and medical attention during the registry period decreased in both groups. However, in the SM+Casperome® group

Table II. Evaluation of the main observed parameters associated with osteomuscular pain.

	Standard Management		Standard Management + Casperome®	
	0 week	4 week	0 week	4 week
1. Local pain on effort (n. of subjects)	27	12	25	6*
2. Pain free walking distance (m)	35.4±9.3	76.3±10.3	34.8±8.2	188±12.7*
3. Joint effusion (n. of subject)	27	16	25	6*
4. Damages/ematomas (n. of subjects)	13	8	12	4*
5. Thermography (differences in C°)	2.7±0.5	2.1±0.4	2.7±0.4	1±0.2*
6. VAS pain (range 0-5)	4.3±0.2	2.8±0.2	4.2±0.3	1.1±0.4*

*$p<0.05$ vs. Standard Management at 4 weeks (control group). All data are expressed as mean ± standard deviation.

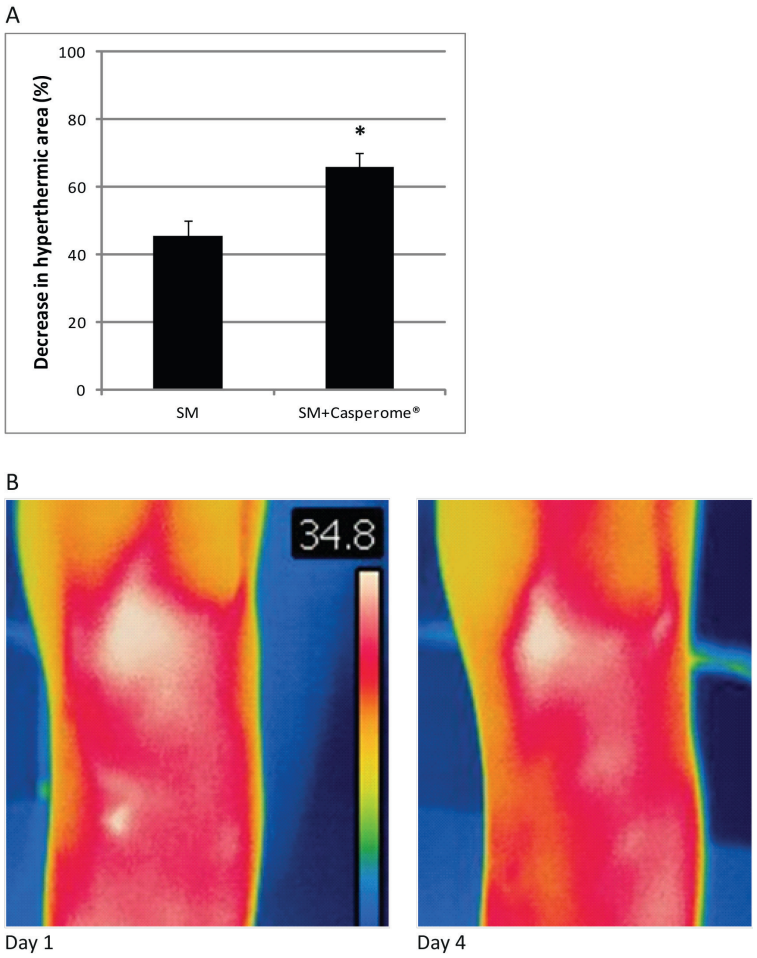

Figure 1. Evaluation of the painful, high-temperature areas in the anterior knee. ***A,*** At 4 week the high-temperature area in the knees of Casperome®-supplemented subjects decreased more than control group. Values are expressed as mean± SD. ***B,*** Infrared image of the anterior knee of a Casperome®-supplemented subject at day 1 and at day 4 of the registry study. The temperature scale applies for each infrared images.

the reduction in the need for other treatments to reduce osteo-muscular pain was significantly greater than in the SM group. At 4 weeks, in the SM+Casperome® group 2 out of 25 subjects had used NSAIDs (vs 9/27 in the control group) (p<0.05). In Table III, we reported a significant decrease of the cartilage damage and inflammation biomarkers (COMP and CRP) at the end of the study, in Casperome® supplemented subjects compared with SM only-treated subjects.

Discussion

This observational registry study provides further evidence on the efficacy of the highly standardized *Boswellia serrata* extract in the management of pain and inflammatory conditions. Previous studies have focused mainly on the effects of BSE in patients with osteoarthritis[20,21,26]. The present study investigated the role played by BSE in the management of osteo-mus-

Table III. Assessment of the circulating biomarkers of cartilage damage and inflammation.

	Standard Management		Standard Management + Casperome®	
	0 week	4 week	0 week	4 week
COMPT (mg/l)	2.87±1.8	2.55±2.3	2.83±0.33	1.95±2.2*
CRP (mg/l)	3.1±0.4	2.11±0.4	3.22±0.8	1.5±0.3*

*p<0.05 vs. Standard Management at 4 weeks (control group). All data are expressed as mean ± standard deviation.

cular pain, particularly acute knee pain, and inflammation, in healthy young rugby players. The use of natural supplements, particularly in young subjects, is an important priority considering the huge burden of traumatic injuries in intense, high contact sports. For instance, knee pain is one of the most prevalent complaints in sport medicine[17,27,28]. For centuries, *Boswellia serrata* has been used in traditional medicine to treat various topical and systemic inflammatory diseases. Given its longtime-recognized healthful effect, BSE became very popular also in Western countries in the last decade. BSE action has been extensively investigated in several researches at different dosages and formulations[2]. Given the poor bioavailability of these compounds, a new formulation (Casperome®) that takes advantage of the Phytosome® technology, has been created[15,16]. The dosage of Casperome® supplementation applied in this registry study (500 mg/day for 5 days and 250 mg/day for 23 days) produced a rapid beneficial effect, in comparison with SM only, on osteo-muscular pain and inflammation parameters. In particular, our results indicate that a short 4-week supplementation with the new delivery form of the standardized *Boswellia serrata* extract (Casperome®) significantly improves the recovery from microtraumas and injuries associated with an intense sport activity. Additionally, the reduction of blood COMP levels suggests a protective effect of Casperome® against cartilage damage, a frequent problem in athletes, and in obese and elderly individuals[29].

In patients with osteo-muscular pain associated with an intense physical activity, analgesic and anti-inflammatory drugs are frequently used. However, important gastrointestinal or cardiovascular adverse effects are associated with long-term (or even acute) use of NSAIDs and corticosteroids[30]. Therefore, a botanical preparation like Casperome® could represent a promising safe anti-inflammatory integrated remedy, particularly in non-severe conditions, for instance, a painful osteo-muscular condition that does not alter normal life but strongly impacts athletic performance.

Conclusions

The management of osteo-muscular pain in frequent, minor, high contact-related sport injuries in otherwise healthy subjects must consider a 'safety-first' approach, particularly for young athletes. Despite all the limitations implicit in any observational analysis, this registry study suggests that Casperome® supplementation could represent an effective and safe, integrated approach for the treatment of osteo-muscular pain and inflammation. Larger scale investigations are needed to further evaluate these promising findings.

Acknowledgements

We warmly thank all the participating volunteers for their engagement in this study. We thank Dr Sara Parodi, Ph.D, who provided medical writing services, supported by internal funds.

Conflicts of interest

FF and TS are employees of Indena SpA. LG is a consultant of Indena SpA.

References

1) [No authors listed]. Boswellia serrata. Monograph. Altern Med Rev 2008; 13: 165-167.
2) Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin Pharmacokinet 2011; 50: 349-369.
3) Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. Eur Rev Med Pharmacol Sci 2015; 19: 1338-1344.
4) Pellegrini L, Milano E, Franceschi F, Belcaro G, Gizzi G, Feragalli B, Dugall M, Luzzi R, Togni S, Eggenhoffner R, Giacomelli L. Managing ulcerative colitis in remission phase: usefulness of Casperome®, an innovative lecithin-based delivery system of Boswellia serrata extract. Eur Rev Med Pharmacol Sci 2016; 20: 2695-2700.
5) Pasta V, Dinicola S, Giuliani A, Harrath AH, Alwasel SH, Tartaglia F, Cucina A, Bizzarri M. A randomized trial of Boswellia in association with betaine and myo-inositol in the management of breast fibroadenomas. Eur Rev Med Pharmacol Sci 2016; 20: 1860-1865.
6) Pasta V, Gullo G, Giuliani A, Harrath AH, Alwasel SH, Tartaglia F, Cucina A, Bizzarri M. An association of boswellia, betaine and myo-inositol (Eumastós) in the treatment of mammographic breast density: a randomized, double-blind study. Eur Rev Med Pharmacol Sci 2015; 19: 4419-4426.

7) Ferrara T, De Vincentiis G, Di Pierro F. Functional study on Boswellia phytosome as complementary intervention in asthmatic patients. Eur Rev Med Pharmacol Sci 2015; 19: 3757-3762.

8) Sferra R, Vetuschi A, Catitti V, Ammanniti S, Pompili S, Melideo D, Frieri G, Gaudio E, Latella G. Boswellia serrata and Salvia miltiorrhiza extracts reduce DMN-induced hepatic fibrosis in mice by TGF-beta1 downregulation. Eur Rev Med Pharmacol Sci 2012; 16: 1484-1498.

9) Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. Cochrane Database Syst Rev 2014; 5: CD002947.

10) Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med 2006; 72: 1100-1116.

11) Safayhi H, Mack T, Sabieraj J, Anazodo MI, Subramanian LR, Ammon HP. Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. J Pharmacol Exp Ther 1992; 261: 1143-1146.

12) Siemoneit U, Pergola C, Jazzar B, Northoff H, Skarke C, Jauch J, Werz O. On the interference of boswellic acids with 5-lipoxygenase: mechanistic studies in vitro and pharmacological relevance. Eur J Pharmacol 2009; 606: 246-254.

13) Siemoneit U, Koeberle A, Rossi A, Dehm F, Verhoff M, Reckel S, Maier TJ, Jauch J, Northoff H, Bernhard F, Doetsch V, Sautebin L, Werz O. Inhibition of microsomal prostaglandin E2 synthase-1 as a molecular basis for the anti-inflammatory actions of boswellic acids from frankincense. Br J Pharmacol 2011; 162: 147-162.

14) Du Z, Liu Z, Ning Z, Liu Y, Song Z, Wang C, Lu A. Prospects of boswellic acids as potential pharmaceutics. Planta Med 2015; 81: 259-271.

15) Semalty A, Semalty M, Rawat MS, Franceschi F. Supramolecular phospholipids-polyphenolics interactions: the PHYTOSOME strategy to improve the bioavailability of phytochemicals. Fitoterapia 2010; 81: 306-314.

16) Hüsch J, Bohnet J, Fricker G, Skarke C, Artaria C, Appendino G, Schubert-Zsilavecz M, Abdel-Tawab M. Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome®) of Boswellia extract. Fitoterapia 2013; 84: 89-98.

17) Kodali P, Islam A, Andrish J. Anterior knee pain in the young athlete: diagnosis and treatment. Sports Med Arthrosc 2011; 19: 27-33

18) Archbold HA, Rankin AT, Webb M, Nicholas R, Eames NW, Wilson RK, Henderson LA, Heyes GJ, Bleakley CM. RISUS study: Rugby Injury Surveillance in Ulster Schools. Br J Sports Med 2015. pii: bjsports-2015-095491.

19) Grover AK, Samson SE. Benefits of antioxidant supplements for knee osteoarthritis: rationale and reality. Nutr J 2016; 15: 1.

20) Belcaro G, Dugall M, Luzzi R, Ledda A, Pellegrini L, Cesarone MR, Hosoi M, Errichi M, Francis S, Cornelli U. FlexiQule (Boswellia extract) in the supplementary management of osteoarthritis: a supplement registry. Minerva Med 2014; 105: 9-16.

21) Belcaro G, Dugall M, Luzzi R, Ledda A, Pellegrini L, Hu S, Ippolito E. Management of osteoarthritis (OA) with the pharma-standard supplement FlexiQule (Boswellia): a 12-week registry. Minerva Gastroenterol Dietol. 2015. [Epub ahead of print].

22) Riva A, Morazzoni P, Artaria C, Allegrini P, Meins J, Savio D, Appendino G, Schubert-Zsilavecz M, Abdel-Tawab M. A single-dose, randomized, cross-over, two-way, open-label study for comparing the absorption of boswellic acids and its lecithin formulation. Phytomedicine 2016; 23: 1375-1382.

23) Ring EF, Ammer K. Infrared thermal imaging in medicine. Physiol Meas 2012; 33: R33-46.

24) Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63: S240-S252.

25) Bedi A, Lynch EB, Sibilsky Enselman ER, Davis ME, Dewolf PD, Makki TA, Kelly BT, Larson CM, Henning PT, Mendias CL. Elevation in circulating biomarkers of cartilage damage and inflammation in athletes with femoroacetabular impingement. Am J Sports Med 2013; 41: 2585-2590.

26) Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee: a randomized double blind placebo controlled trial. Phytomedicine 2003; 10: 3-7.

27) Di Matteo B, Filardo G, Lo Presti M, Kon E, Marcacci M. Chronic anti-platelet therapy: a contraindication for platelet-rich plasma intra-articular injections? Eur Rev Med Pharmacol Sci 2014; 18: 55-59.

28) Perdisa F, Filardo G, Di Matteo B, Di Martino A, Marcacci M. Biological knee reconstruction: a case report of an Olympic athlete. Eur Rev Med Pharmacol Sci 2014; 18: 76-80.

29) Maremmani I, Gerra G, Ripamonti IC, Mugelli A, Allegri M, Viganò R, Romualdi P, Pinto C, Raffaeli W, Coluzzi F, Gatti RC, Mammucari M, Fanelli G. The prevention of analgesic opioids abuse: expert opinion. Eur Rev Med Pharmacol Sci 2015; 19: 4203-4206.

30) Guidolin D, Franceschi F. Viscosupplementation with high molecular weight native hyaluronan. Focus on a 1500-2000 KDa fraction (Hyalubrix®). Eur Rev Med Pharmacol Sci 2014; 18: 3326-3338.