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# Effectiveness of a novel boswellic acids delivery form (Casperome®) in the management of grade II ankle sprains due to sport trauma – a registry study

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**Abstract. – OBJECTIVE: In this study, we evaluated a novel delivery form of boswellic acids (Casperome®) in the management of signs and symptoms associated with ankle sprain grade II due to sport trauma.**

**PATIENTS AND METHODS: In this supplement registry study, 72 otherwise healthy subjects with grade II ankle sprain induced by sport activities were advised to either follow a standard management (SM, 37 subjects) for the condition or the SM with the additional daily intake of 1 tablet containing 250 mg Casperome® (35 subjects). Subjects were allowed to use rescue medications (ketoprofen tablets, 25 mg/tablet), and their intake was measured at the end of the management period of 7 days. Each individual was subjected to several non-invasive examinations (self-reported *pain at rest and under moderate exercise, range of active and passive movement, presence of local hematomas by ultrasonography*) at the following time periods: at inclusion, to evaluate the basal conditions of the subject before the beginning of the study, at day 3 and at the end of the week to evaluate the response differences between the two groups. Additionally, a blood sample from the Casperome® treated subjects (34 out of 35 subjects) was taken at day 7 and analyzed for the systemic concentration of boswellic acids.**

**RESULTS: The 72 individuals recruited in this study spontaneously decided which management to follow, either SM (n=37) or SM+Casperome® (n=35). Supplementation with Casperome® 250 mg/day showed beneficial effects in the reduction of signs and symptoms of ankle sprains evaluated at day 3 and day 7, and was shown to induce measurable plasma level of boswellic acids. Moreover, the supplementary use of Casperome® was well-tolerated and devoid of side effects.**

**CONCLUSIONS: Our pilot registry study showed the effectiveness of Casperome® supplementation in improving recovery after ankle sprain of mild severity (grade II), suggesting a potentialy beneficial role in relieving the trauma associated with sport activities and in decreasing the use of rescue drugs.**

Key Words:
Ankle sprain, *Boswellia* serrate extract, Boswellic acids, Inflammation, Pain.

## Introduction

Sprains (specifically those involving ankle/knee) are characterized by stretching or tearing of non-contractile structures (ligaments or joint capsules). Ligamentous (sprain) and muscular (strain) injuries may be classified according to the degree of impairment: grade I sprain is characterized by stretching (without tearing) of the ligament, local tenderness, minimal edema, no gross instability with stress testing and a firm endpoint; grade II sprains are partial tears of the ligaments, with moderate local tenderness, mild instability with stress testing and a firm endpoint (this lesion is moderately incapacitating); grade III sprains present a complete tear, with discomfort at manipulation, a variable amount of edema and swelling (from absent to conspicuous), clear instability


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at stress testing (with a mushy endpoint), accompanied by severe disability[1-3]. Early mobilization is recommended for the management of low-grade ankle sprain whenever possible: although both immobilization and early mobilization prevent late residual symptoms and ankle instability, early mobilization allows to resume routine daily activities and may be more comfortable for patients. In addition, early mobilization can prevent the onset of vascular complications, including vein thrombosis[4,5]. Several management strategies[6-14] including topical or systemic non-steroidal anti-inflammatory drugs (NSAIDs) are used for sprains, soft tissue injuries and sports trauma. However, systemic adverse events (mainly intestinal ulcers, gastrointestinal disturbance and hemorrhage) are reported with a not-negligible frequency with the oral administration of NSAIDs. To overcome these issues, some studies have tested, with positive results, the efficacy and tolerability of local managements[15-18], which offer the advantage of a drug delivery to the local affected tissues maintaining low plasma levels and controlling the occurrence of systemic adverse events with usually minimal tolerability issues. Notably, some of these studies have included patients suffering from painful, benign (grade I) ankle sprains as a model of general traumatic soft tissue injuries. The primary efficacy criterion was spontaneous pain change after 7 days of management in the intention-to-treat population[19]. Without neglecting the important contribution represented by synthetic anti-inflammatory drugs, there are several botanical extracts, such as *Boswellia serrata* gum resin extract containing boswellic acids (BAs) as the main bioactive ingredients, which have been proven effective in the management of pain and inflammation, including that deriving from sport traumas[20-23]. Based on previous pharmacokinetics studies, Bas - when administered as Casperome® (lecithin delivery system) - have been documented to possess a long half-life, thus supporting a once-daily administration with biologically active plasma levels of the target compounds[24]. Following these previous experiences, we decided to the test in the present work if the oral use of Casperome® (250 mg once daily) is helpful, when combined with SM, in improving signs and symptoms, patients' mobility and exercise/training ability in grade II sprains as a model for sport injuries, soft tissue damage and local trauma associated with pain and reduced mobility.

## Patients and Methods

### Patients and Procedures

Subjects with grade II ankle sprain (partial tears of the ligaments, moderate local tenderness, mild instability but firm endpoint) were recruited; the lesion was moderately incapacitating. Individuals with grade III sprains (complete tear, discomfort with manipulation, swelling and edema, clear instability and severe disability) were excluded. The extension of the sprains, accompanied by subcutaneous visible changes as hematomas, was neither larger nor longer than 6×6 cm, with a thickness of the affected area (if hematoma was present) not >1 cm. This evaluation was made by high-resolution ultrasound at the first visit. One main single target lesion for each patient was considered. Therefore, subjects with multiple sprains/contusions or bleeding, limb ulcerations and infections were excluded. The sprains were all located at the ankle and the inclusion of the patients was completed within 24 h after the injury. Ice packs and non-drug local managements were allowed only within 12 h after the trauma, before inclusion. Patients in need of immobilization or invasive orthopedic procedures, or those with complex lesions were excluded, as well as all patients using any drug for any clinical problem. Similarly, patients with other inflammatory/post-traumatic problems (strains, contusions, tendonitis, bursitis) were excluded. Full immobilization (which is usually not prescribed or recommended for this type of injury) was avoided and a light elastic bandage was used in all subjects. Selection in the study involved only acute, uncomplicated ankle sprain of grades II seen within 24 h after a sport injury. Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, pre-therapeutic applications. "Supplement studies" produce supplementary data to be compared with those from the best available management plans. These types of studies are performed using pharmaceutical standard supplements with high level of safety and standardization[25-27] considering safety and tolerability as the first items. All participants gave written informed consent before enrolment. The study protocol was approved by the local Ethical Committee.

### Management

The usual management for a simple sprain is defined by the acronym R.I.C.E. (rest, ice, compression, elevation), while a more complex lesion (i.e. a torn ligament) may require immo-

bilization or surgery. In our study R.I.C.E. for 7 days represented the standard management (SM), with the addition of a dynamic fixation (Tensoplast® bandage, Sixtus, Prato, Italy) limiting the lateral mobility and controlling the swelling and hematomas. A second group received, in addition to SM, a tablet of Casperome® (Indena SpA, Milan, Italy) (250 mg/day in a single administration) for the same period of time (7 days after the trauma).

The primary endpoint was the assessment of pain reduction (on a visual analogue line scale; VAS) upon active motion, while the evaluation of pain reduction at rest (VAS) represented the secondary end point.

The following clinical and instrumental tests were performed:

- Evaluation by patients: pain at rest and during active movement were measured with a VAS, a 100 mm horizontal line with "0 = no pain" at the left side and "100 = extreme pain" at the right side. The evaluation was carried out daily by the patient;
- Evaluation by the physician: pain at rest, during active and passive movements (and their impairment) were also measured by the physician in charge on a VAS scale. The evaluation was carried out at the enrollment and after 1 week;
- 'Minimal' effort test: an effort test was performed – if possible - at inclusion and at 7 days to evaluate the impairment due to the lesion. A 'minimal', walking treadmill test (3 Km/h with 10% inclination for 3 min) was used. The effects of pain and altered function on the exercise performance were assessed on a linear scale (0-10) where 10 was the best possible performance and 0 represented the total impossibility to initiate and complete the test (i.e. due to pain);
- Ultrasound: the presence of vascular problems (i.e. superficial thrombosis, hematoma) was excluded by a duplex investigation (particularly excluding venous thrombosis and peripheral vascular disease). Patients with vascular impairment/problem and thrombosis were excluded. The presence of local hematomas was also evaluated and quantified (in volume, ml) measuring presence, size and thickness of the hematoma/s;
- Analysis of plasma levels of BAs: blood was collected from 34 out of 35 volunteers at day 7 and analyzed according to the method previously described for the measurement of the six major BAs (11-keto-β BA, KBA; acetyl-11-keto-beta-BA, AKBA; β-BA; α-BA; acetyl-**β**-BA; acetyl-**α**-BA)[24]. Each 12 ml sample was collected into tubes containing Li-heparin and was rapidly centrifuged at 3000 rpm for 10 min. Immediately after the centrifugation, about 2.5 ml of plasma from each sample were transferred to polypropylene tubes and frozen at -20°C. The BAs content in plasma samples was determined using a sensitive previously developed and validated LC-MS method[28,29].

### Statistical Analysis

Non-parametric statistical analysis was used, as most measurements were non-parametric. A group of at least 15 subjects was considered, to have meaningful results. Comparisons of numerical data were performed by Student *t*-test and ANOVA test with post-hoc Bonferroni's correction, as appropriate. A $p$-value $<0.05$ was considered statistically significant.

## Results

Table I shows details of the patients with ankle sprain (grade II) and Table II and Figure 1 show the primary and secondary endpoints assessed at inclusion, at day 3 and day 7, respectively. The comparative evaluation between groups indicated a better efficacy of the combined management including Casperome®; the variations in the control group were broadly comparable with the natural evolution of grade II ankle sprain and, therefore, the contribution of the management was limited. The efficacy of Casperome® in speeding-up the recovery was significantly higher than the control management for all included parameters. Also subjective and investigator's evaluation of tolerability was optimal in the combined management group. No side effects or

**Table I.** Details of the study group.

| Group | Total, number | Male/Female | Age, mean±SD |
|---|---|---|---|
| SM | 37 | 18/19 | 33.5±2.4 |
| SM + Casperome® | 35 | 18/17 | 32.5±2.4 |

**Table II.** Primary and secondary endpoints assessed at inclusion, at day 3 and at day 7.

| | | Inclusion | Day 3 | Day 7 |
|---|---|---|---|---|
| Primary parameter (VAS) | | | | |
| Pain (VAS 0-100 mm) – spontaneous | SM+Casperome® | 73.3±5.4 | 42.2±3* | 29.4±3.5* |
| | SM | 74.4±3.2 | 68.4±2.1 | 45±2.5 |
| Pain (VAS 0-100 mm) – in motion | SM+Casperome® | 87.4±5.2 | 31.2±2* | 22.3±3.5* |
| | SM | 86±3.3 | 67.3±3 | 41±3.2 |
| Secondary parameters | | | | |
| Volunteers with complete resolution (%) | SM+Casperome® | | | 78.3 |
| | SM | | | 38.4 |
| Joint swelling reduction (scale 100% to 0%) | SM+Casperome® | 100 | 34.5±2.3* | 30±2.4* |
| | SM | 100 | 67.3±2.2 | 58±3.1 |
| Impaired mobility (10=immobility; 0=full mobility) | SM+Casperome® | 8.8±0.6 | 4.2±0.7* | 2.1±0.6* |
| | SM | 8.9±0.6 | 7.5±1.1 | 4.3±2 |
| Volunteer's efficacy assessment (0-10) | SM+Casperome® | | | 8.2±1† |
| | SM | | | 6.5±1.6 |
| Investigator's efficacy assessment (0-10) | SM+Casperome® | | | 8.8±0.2† |
| | SM | | | 7.1±0.4 |
| Tolerability evaluation/ | | | | |
| Safety evaluation | SM+Casperome® | | | 9±0.4 |
| | SM | | | 8±1 |
| Use of rescue medication (patients and total tablets) | SM+Casperome® | | | 2/18 (4 tabs)† |
| | SM | | | 7/18 (22 tabs) |

Data are expressed as mean ± standard deviation. *$p$ <0.05 vs. inclusion. †$p$ <0.05 vs. SM group.

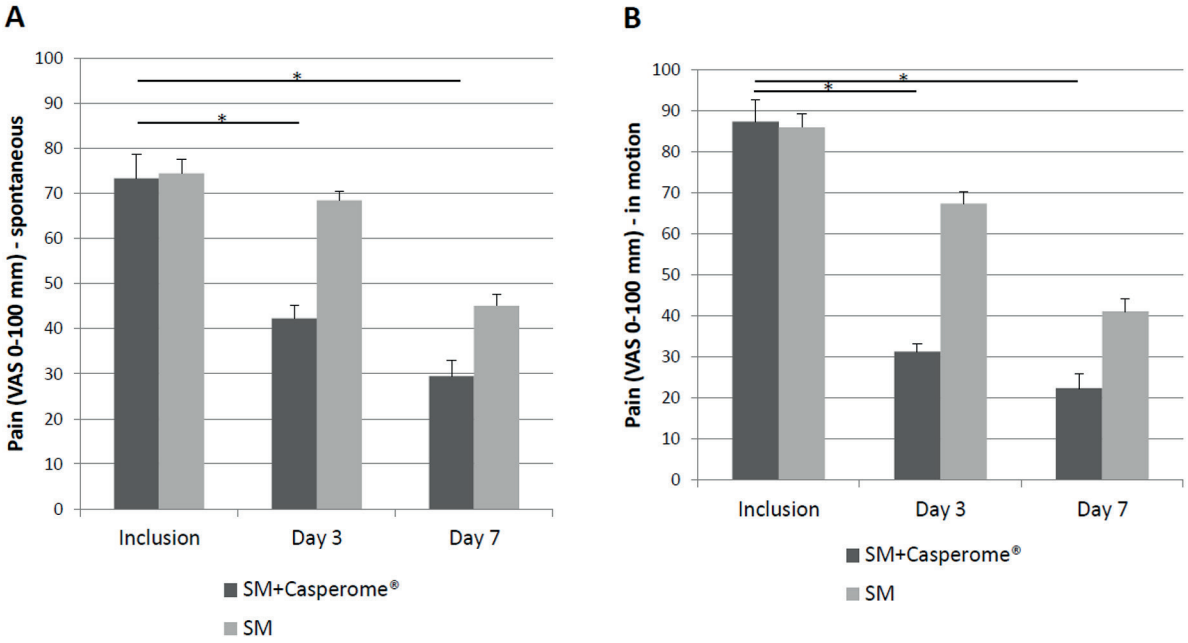


**Figure 1.** Spontaneous and in motion pain assessed by Visual Analogue Scale (VAS).

gastrointestinal problems associated with Casperome® were observed. The plasma levels achieved with Casperome® are reported in Table III and confirm the presence of the maior BAs, except AKBA, in the plasma of the volunteers.

## Discussion

Distortions, contusions, sprains and strains are among common consequences of walking or running accidents and sports injuries.

**Table III.** Boswellic acids content in 34 plasma samples of volunteers in the SM+Casperome®

| Sample name | KBA results [ng/mL] | AKBA results [ng/mL] | α-BA results [ng/mL] | β-BA results [ng/mL] | Acetyl- α -BA results [ng/mL] | Acetyl- β-BA results [ng/mL] |
|---|---|---|---|---|---|---|
| N-1 | 12.60 | < LOQ | 147.94 | 350.12 | 159.71 | 323.73 |
| N-2 | 27.48 | < LOQ | 110.76 | 296.92 | 81.79 | 196.97 |
| N-3 | 21.57 | < LOQ | 141.82 | 354.38 | 141.41 | 355.22 |
| N-4 | 40.44 | < LOQ | 117.78 | 293.17 | 76.32 | 173.36 |
| N-5 | 80.84 | < LOQ | 189.21 | 487.93 | 121.63 | 300.47 |
| N-6 | 32.40 | < LOQ | 189.24 | 425.09 | 37.08 | 74.82 |
| N-7 | 73.47 | 7.17 | 229.62 | 579.48 | 100.71 | 324.77 |
| N-8 | 32.73 | < LOQ | 198.05 | 459.44 | 37.13 | 73.87 |
| N-9 | 34.12 | < LOQ | 178.42 | 512.42 | 88.65 | 266.38 |
| N-10 | 8.07 | < LOQ | 101.17 | 258.74 | 43.85 | 116.87 |
| N-11 | 66.00 | < LOQ | 260.95 | 611.63 | 79.77 | 251.70 |
| N-12 | 15.44 | < LOQ | 112.18 | 283.34 | 30.73 | 121.66 |
| N-13 | 98.33 | 7.02 | 272.03 | 668.42 | 97.81 | 331.46 |
| N-14 | 70.46 | < LOQ | 589.32 | 1389.65 | 286.14 | 849.89 |
| N-15 | 73.65 | < LOQ | 346.25 | 851.31 | 181.00 | 546.69 |
| N-16 | 56.68 | < LOQ | 522.58 | 1301.39 | 337.77 | 804.81 |
| N-17 | 25.14 | < LOQ | 147.02 | 399.42 | 84.12 | 237.25 |
| N-18 | 5.44 | < LOQ | 168.40 | 442.80 | 97.96 | 264.70 |
| N-19 | 29.53 | < LOQ | 154.69 | 424.74 | 82.73 | 264.10 |
| N-20 | 7.17 | < LOQ | 188.00 | 473.45 | 87.29 | 261.03 |
| N-21 | 9.24 | < LOQ | 249.97 | 340.62 | 137.70 | 473.32 |
| N-22 | 52.97 | < LOQ | 187.92 | 421.74 | 74.04 | 199.27 |
| N-23 | 9.44 | < LOQ | 263.03 | 349.10 | 194.05 | 462.11 |
| N-24 | 55.68 | < LOQ | 240.81 | 534.24 | 101.78 | 231.12 |
| N-25 | 71.71 | < LOQ | 222.55 | 516.32 | 167.16 | 365.72 |
| N-26 | 29.88 | < LOQ | 163.03 | 352.75 | 75.70 | 131.41 |
| N-27 | 59.42 | < LOQ | 167.90 | 413.89 | 121.57 | 282.30 |
| N-28 | 24.82 | < LOQ | 148.88 | 331.95 | 62.24 | 117.08 |
| N-29 | 24.92 | < LOQ | 167.93 | 405.32 | 110.55 | 240.85 |
| N-30 | 71.05 | < LOQ | 240.55 | 543.67 | 99.94 | 183.86 |
| N-31 | 17.06 | < LOQ | 122.15 | 330.95 | 68.27 | 166.09 |
| N-32 | 155.42 | < LOQ | 502.53 | 1103.33 | 275.94 | 591.86 |
| N-33 | 90.52 | < LOQ | 441.04 | 1020.27 | 195.44 | 673.31 |
| N-34 | 103.34 | < LOQ | 212.52 | 489.65 | 128.46 | 316.69 |

LOQ for KBA and AKBA: 5 ng/ml; LOQ for the other: 0.5 ng/ml; LOQ = limit of quantification.

Symptoms of such traumatic injuries are severe pain, edema and hematomas and – in the case of joint injuries extended to the capsule – strains or even fracture. Pain, swelling and impairment of mobility tend to increase with inflammation processes. Although the severity of ankle sprain is commonly classified as grade I to III, also mild conditions can often be painful, altering mobility and causing further problems. Due to its frequency, acute ankle trauma is a common and costly cause of visits to physicians or emergency departments, and produces a significant loss in working days. Symptomatic management consists of rest, ice, compression and elevation. Currently the most commonly prescribed drugs (for the management of some symptoms) are oral paracetamol or NSAIDs, including aspirin, although they may present some side effects. Early mobilization – particularly in younger subjects – is considered very important for the optimal healing. In addition to rapid pain relief, an essential starting point for therapy is the inhibition of inflammation at the site of injury. Complication and temporary disabilities could be the consequences of improperly treated or untreated ankle sprains. In our study, we demonstrated the effectiveness of Casperome® together with SM and with the possibility to use rescue medications, as a supplementary strategy with an excellent safety profile in the recovery after ankle sprain grade II. Casperome® is a highly purified extract, obtained from the phytosome delivering form of resin of *Boswellia serrate*

(frankincense). Several *in vitro* and *in vivo* studies, and pilot clinical trials support the potential of *Boswellia serrata* gum resin extract for the management of a various inflammatory diseases such as bowel disease, rheumatoid arthritis, osteoarthritis and asthma[23,30-32]. In a recent study[23], we demonstrated the efficacy of a novel high-bioavailability delivery form of boswellic acid in the management of musculoskeletal pain in young rugby players, with an excellent tolerability and the absence of gastrointestinal side effects. In this work we were able to confirm the relief of pain in an additional traumatic sport condition paralleled by the presence of biologically active circulating levels of BAs in subjects supplemented with a daily dosage of 250 mg.

## Conclusions

The management of grade-II ankle sprains may benefit from oral Casperome® administration at 250 mg/day: in the group using Casperome® supplementation the injuries improved better and faster, with a significantly increased control of pain and function.

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### Conflict of interest

ST and AR are employees of Indena S.p.A. LG is a consultant of Indena S.p.A. The other Authors declare no conflicts of interest.

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