

## ORIGINAL ARTICLE

# Supplementation with a new food grade delivery system of *Boswellia* and *Centella* in the intervertebral discs registry: the Sager study

Hosoi MORIO <sup>1,2,3</sup>, Maria R. CESARONE <sup>1,2,3</sup>, Gianni BELCARO <sup>1,2,3</sup> \*, Beatrice FERAGALLI <sup>1,2</sup>, Roberto COTELLESE <sup>1,2</sup>, Shu HU <sup>1,2,3</sup>, Mark DUGALL <sup>1,2,3</sup>, Claudia MAIONE <sup>1,2,3</sup>, Valeria SCIPIONE <sup>1,2,3</sup>, Claudia SCIPIONE <sup>1,2,3</sup>, Antonella RIVA <sup>4</sup>, Giovanna PETRANGOLINI <sup>4</sup>, Stefano TOGNI <sup>4</sup>

<sup>1</sup>Irvine3 Labs, Pescara, Italy; <sup>2</sup>Department SMO Biotec, Chieti-Pescara University, Pescara, Italy; <sup>3</sup>IAPSS, Pescara, Italy; <sup>4</sup>Indena SpA, Milan, Italy

\*Corresponding author: Gianni Belcaro, Irvine3 Labs, Department SMO Biotec, Chieti-Pescara University, IAPSS, Pescara, Italy. E-mail: [cardres@abol.it](mailto:cardres@abol.it)

## ABSTRACT

**BACKGROUND:** The aim of this registry study was to investigate the potential of a new food-grade formulation of the association of *Boswellia serrata* and *Centella asiatica* extracts (*Boswellia/Centella* Phytosome, [BCP]) in combination with standard management (SM) to produce a faster re-expansion of the intervertebral disks in symptomatic subjects with “flattened” disks in the lower spine, due to wrong posture and compression after repeated trauma.

**METHODS:** The study was designed as a 3-6 months pilot registry. Three groups of subjects were comparable for characteristics and symptoms at baseline: SM+BCP; SM; SM+glucosamine.

**RESULTS:** No side effects were observed. Regarding target measurements at 3 and 6 months, height increased in the BCP group vs. the other two groups. The total spine length improved in the BCP group ( $P<0.05$ ); in particular at 6 months the increase was doubled with BCP. SM was effective in producing elongation but the association with BCP made spinal elongation faster, more effective, with a better expansion of the intervertebral disks. Regarding ultrasound measurements, BCP was able to significantly ameliorate the posterior disk space ( $P<0.05$ ) and decreased disk density more than the other groups of the study. Signs/symptoms and mobility were improved with BCP ( $P<0.05$ ), while rescue medications decreased. The loss of working days was reduced with all managements (significantly more in BCP group than in the other two).

**CONCLUSIONS:** The relative effects on spinal elongation, disk space, signs/symptoms of BCP appeared to double the efficacy of SM, improving symptoms associated to a very good tolerability of BCP.

(Cite this article as: Morio H, Cesarone MR, Belcaro G, Feragalli B, Cotellese R, Hu S, *et al.* Supplementation with a new food grade delivery system of *Boswellia* and *Centella* in the intervertebral discs registry: the Sager study. Panminerva Med 2022;64:48-55. DOI: 10.23736/S0031-0808.20.04028-8)

**KEY WORDS:** Spinal cord compression; Intervertebral disc; Osteoarthritis; Ultrasonography; *Boswellia*; *Centella*.

Spinal problems and intervertebral disks (IVD) alterations are common and frequently associated to nerve compression and symptoms due to neurological impairment particularly at the spinal roots. Pain, muscular numbness, paresthesias, altered mobility cause important chronic problems with loss of working days.

The important issue in spinal nerve compression is due to a decrease in thickness of the spinal disks with approximation of the vertebral bodies. Compression, weight-related physical stress, postural causes, a sedentary life and re-

peated traumas are involved in a progressive reduction of the disk thickness, particularly at the lower lumbar/sacral segments where the combined effects of weight and gravity are cumulated.

In patients with spinal compression symptoms the disks can be reduced to a limited, flattened space and the IVD may have lost most of its initial spongiform/hydrogel structure associated to elasticity, shock absorbing characteristics and to their role in keeping the spinal bodies adequately separated to avoid friction or compression on the nerve structures.<sup>1-3</sup>

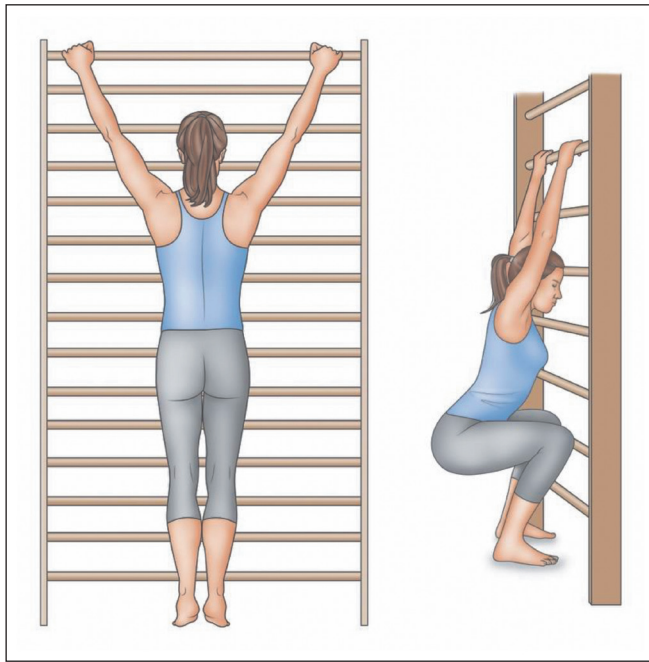


Figure 1.—Examples of extension of the spine which leads to recovery of disks morphology and to an elongation of the spinal length. Even a minimal amount of exercise (on a simple espalier) may improve signs/symptoms of compression in few days if not other problems are present.

Disk morphological structure and its composition can be positively modified if chronic pressure, wrong chronic posture and fixed positions for hours, are relieved *i.e.* by traction, physio or swimming or by methods that extend spinal length, passively or actively with specific exercises.

As shown in Figure 1, the best and simplest actions may improve spinal length and restore disk thickness, structure and perfusion. The active actions, especially in young otherwise healthy subjects, are more effective than any form of physiotherapy. Symptoms of spinal compression at the lower spine may be specifically localized and irradiated to the legs, as shown in Figure 2.

Particularly in younger, otherwise healthy subjects the most common situations involving disk flattening (without major alterations of the vertebral bodies) affect the lower spine (lumbar and sacral segments) with well localized symptoms, at first present only temporarily, and then becoming chronic.

If the vertebral bodies are intact or without major abnormalities or deformations, the disk is flattened (having lost by compression its supporting elastic structure, gel and hydration, affecting also the perfusion). It is possible in most subjects to restore a ‘normal’ disk thickness and function. Restoring the disks structure may relieve nerve compression

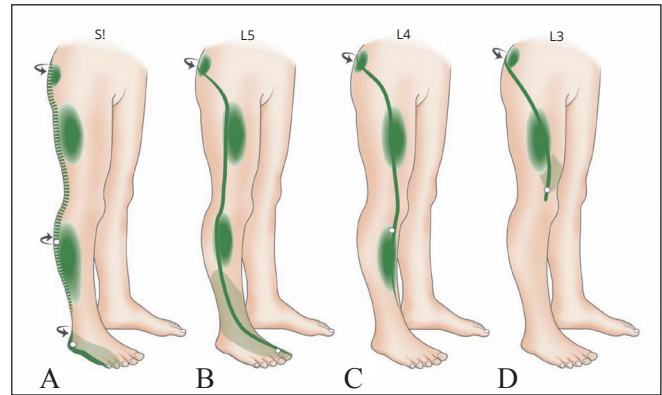


Figure 2.—Representation of the localization of symptoms due to spinal compression at the lower spine. The thick green lines represent the sharp radiating reticular pain with a dermatomal pattern. The dotted lines indicate the location of the numbness or tingling sensations. Disc level: A) sacral (S1); B-D) lumbar (L5-4-3).

sion and symptoms by reducing the causes of compression and improving the disk original structure, perfusion and hydration.

The disk can also be chronically inflamed and traumatized, and the decrease of compression and reshaping of the spine may affect this process cause of local pain and more chronic damage to the disk structures.

Sager’s intuition (P Sager, Director of Dept. M, Orthopedic and Vascular surgery, Bispebjerg Hospital Copenhagen) suggested that the flattening of the intervertebral disks and the shortening of the spine could be reversible (at least in younger, healthy subjects).<sup>4</sup>

These spinal alterations according to historical archeological findings had been present for a very long time and could be caused by compressive actions (*i.e.* due to weights) and, partially, to inflammatory and degenerative conditions, even in subjects hunting in northern Europe in pre-Roman periods.

Considering Sager’s theory of the reversibility of the flattening of the intervertebral disks, nutrition support may be of benefit. For this registry study the potential role of a new food-grade delivery formulation of the association of highly standardized *Boswellia serrata* and *Centella asiatica* extracts (BCP) in association with a specific elongation program was evaluated for the relief of spinal problems and intervertebral disks (IVD) alterations.

*Boswellia serrata* have been used in traditional medicine in India and African countries as a remedy for the treatment of a variety of inflammatory diseases.<sup>5</sup> Interesting data on the effects of *Boswellia serrata* extracts and its active components, boswellic acids, are showed in pre-clinical and clinical studies.<sup>6-8</sup>

*Centella asiatica*, also known as “gotu kola,” is native to the wetlands of Southeast Asia and has been used for centuries in traditional medicine because of its anti-bacterial, anti-viral, anti-hypertensive, diuretic, antiulcer, anti-inflammatory, sedative, anxiolytic and antioxidant properties.<sup>9, 10</sup> *C. asiatica* is also particularly beneficial on tissue repair and microcirculation.<sup>11</sup>

Based on these data, the combination of *Boswellia* and *Centella* extracts formulated as BCP in association with a specific exercise program and with a careful risk factors control may help producing a faster re-expansion of the intervertebral disks in symptomatic subjects with ‘flattened’ disks, at the lower spine, due to wrong posture, compression, repeated minimal trauma (weight bearing).<sup>12</sup>

The registry was aimed at a comparison between the re-elongation of the spine, an improvement in disk structure and a reduction/control in signs symptoms in a 3 to 6 months pilot, concept study.

## Materials and methods

### Registry study design

This was a small-scale, independent, pilot, registry supplementation study. Supplement studies are defined the field of activity of supplements and possible preventive, preferably non-clinical applications.<sup>13-17</sup> These studies are designed and organized with the complete awareness and participation of the enrolled subjects. The best field of application for supplements are pre-disease, borderline applications or the supplementary management of some risk conditions. Unless specific claims are present, supplements are not generally used for treatment of severe signs/symptoms or conditions of clinical relevance. Supplement studies are open-label studies with no placebo. Patients are always informed about the supplement or any treatment and management measure they will receive, and the products under evaluation are not prescribed but recommended. In these types of studies, control groups, if present, are not necessarily parallel.

### Subjects

Otherwise healthy subjects not using any drug were included, with lower back localized pain and signs symptoms of lumbar, spinal compression confirmed by electromyography and present for at least 3 months. The basal irradiation of symptoms was as reported in Figure 2B-D. Only minor X-ray changes at the vertebral bodies had been found. Other characteristics were pain at rest, paresthesia,

loss of limb strength, bilateral but with a mono-lateral prevalence. Pain was only partially relieved by night rest. All subjects had reported altered sleep due to pain.

Problems had also been associated to sitting/working or standing for hours. The Body Mass Index (BMI) at inclusion was <26. Any other neurological disease had been excluded. Subjects had complained of sitting in their office chair and/or car, at least 6 hrs. daily. They all had a minimal exercise pattern or time spend in physical activities. They all used to carry weights at work and at home, most of the day, and very frequently. A mostly sedentary habits characterized all included subjects. Taller subjects (former volleyball or basketball and rugby players) were recruited as observable changes would be possibly larger.

### Supplementation

The supplementation included *Boswellia/Centella* Phytosome® (BCP) in association with a standard management (SM) plan (group A) and compared with only SM (group B) and SM+glucosamine sulphate (900 mg/die in 2 doses – 2 capsules of a generic preparation) (group C).

### Dietary supplement

The dose of BCP included 2 tablets/die, at the dosage of 500 mg each, supplemented one in the morning and one in the evening for 3 to 6 months.

For the registry study, 500 mg of the new food grade sunflower lecithin-based formulation of *Boswellia serrata* and *Centella asiatica* standardized extracts was prepared by Indena S.p.A., as film-coated tablets, corresponding to a content of 18-22% w/w of *Boswellia* extract (standardized to ≥65.0% of total triterpenes by HPLC assay) and 18-22% w/w of *Centella* extract (standardized to contain ≥45.0% of total triterpenes by HPLC assay). Before releasing, the film-coated tablets were tested for appearance, average mass, uniformity of mass, HPLC-content of *Boswellia* and *Centella* extracts, disintegration time and microbiological quality.

### Standard Management

SM corresponded to weight control, spine elongation exercises (espalier, 5 min twice daily), avoiding sitting for more than 1 hour (with 5 minutes walking/standing breaks), positional changes, more rigid mattress, diet reducing calories, salt (NaCl) and sugars, adequate hydration and vitamins, walking at least 20 minutes daily, adequate shock-absorbing shoes, postural chairs.

In particular:



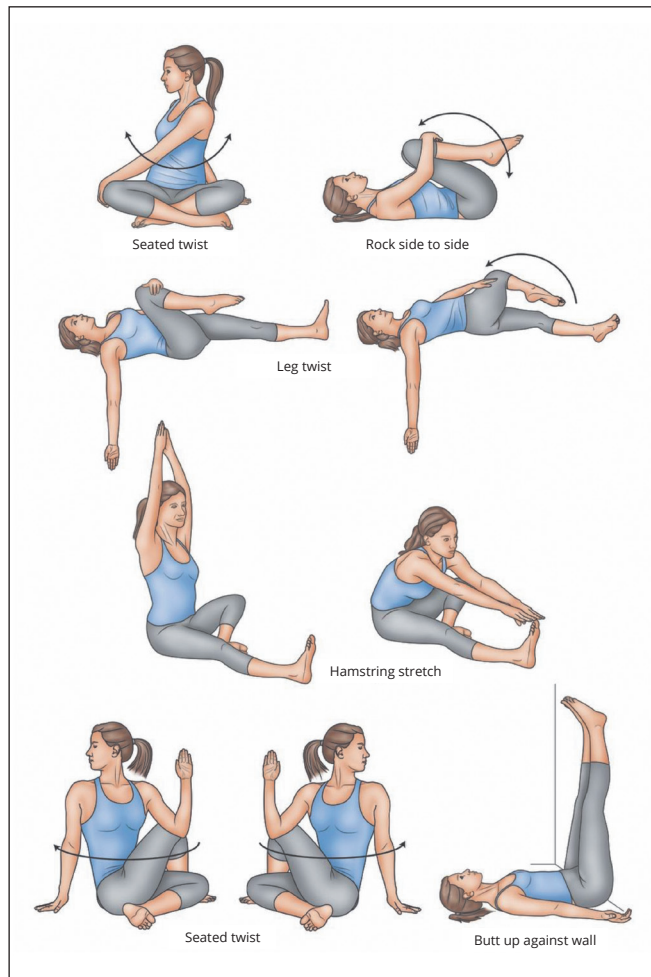


Figure 3.—The second set of exercises included poses for flexibility, back pain and disk mobilization. Exercise plan 2 was followed by all subjects after one month of spinal extensions, without forced positions, at home, at least 4 times/week.

- the exercise plan 1 (elongation) was mainly to expand the disks and elongate the spine;
- the second set of exercise included poses for flexibility, back pain and disk mobilization.

Exercise plan 2 represented in Figure 3 was followed by all subjects after one month of spinal extensions, without forced positions, at home, at least 4 times/week.

#### Target measurements

The main target measurements were:

- the height on flat surface measured in the morning (before 10 a.m.) after a few minutes of resting flat;
- spine length (the total spine length) measured by a spine X-ray.

An average for these subjects (taller subjects with about or more than 180 cm in height) is around 569.4 mm with SD 17.67.<sup>2,3</sup> The total spine length was calculated as the sum of all central vertebral body heights plus the intervertebral disc heights from C3 to L5.

Subjects taller than 180 cm (men) and 175 cm (for women) were included as in taller subjects, spinal elongation is generally more visible and measurable (about 2-4%).

Other ultrasound measurements were:

- posterior disk space measured considering the ultrasound window visible at L1 to L3 (as 3 sampling spaces, averaged in mm);
- disk density measured as a percent decrease, indicating more hydration (on the grey scale median or GSM). The percent indicates the white (echogenic) percentage (GSM) in disk samples. The increase in hydration (due to expansion and increase in water content) decreases GSM. The black parts on ultrasound have the density of blood/water; white is the density of collagen. A disk becoming more expanded, perfused and hydrated becomes darker (more black components, more water inside);
- signs/symptoms measured with a score on a Visual Analogue Scale line (from 0 to 4; with 0 as no symptoms and 4 indicating symptoms inducing to hospital admission or important treatments and immobility);
- general mobility, measured on a visual analogue scale line (from 0 immobility; to 4 normal mobility without restrictions) was recorded;
- rescue medications (namely, diclofenac cp 50 mg for each dose) that were needed in 6 months of follow-up were recorded on a diary with the loss of working days in 6 months due to the spinal problems.

Routine blood tests and inflammatory test (as C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) were also performed and resulted normal at inclusion and at 3 and 6 months. Also tests of hepatic/kidney function were performed, resulting normal at inclusion and 6 months.

#### External study reviewers

All results and data were evaluated by an external reviewing panel, not in contact with the registry patients. Safety and tolerability were assessed by weekly contacts and laboratory measurements as described above. Possible adverse experiences were evaluated throughout the registry in terms of intensity (mild, moderate or severe), considering duration, seriousness, outcome and relationship to the study supplement or concomitant medication.

Statistical analysis

Data and results were analyzed in comparison with the results from the SM considered as a baseline.<sup>18, 19</sup> All measurements were considered not regularly distributed and therefore, non-parametric. Intra- and inter-group comparisons were performed by non-parametric tests and using the ANOVA test, as appropriate. A P value <0.05 was considered statistically significant. These results are not parametric. According to previous studies on comparable groups, at least 10 subjects were considered adequate to define a difference in target outcomes after at least 3 to 6 months of supplementation.

Results

The 3 groups of registry subjects, as reported in Table I, resulted comparable for physical characteristics and symptoms distribution. No side effects were observed in the subjects using the supplementations. The tolerability was optimal, and no subject had to stop supplementation.

Main target measurements

Height (on flat surface) was increased in the BCP group more than in the other two groups (P<0.05) at 3 and 6 months (Table II).

The total spine length (TSL) was also increased more in the BCP supplementation group at 3 and 6 months (P<0.05); at 6 months, the TSL increase was 41;4 mm with the BCP supplementation and about half of this measure in the other two groups (P<0.05). The SM is effective in producing elongation but the supplementation with BCP made spinal elongation faster and more effective, with a better expansion of the intervertebral disks.

TABLE I.—Participants' characteristics.

Group	Allocation	Parameters	Inclusion	3 months	6 months
A	SM+BCP	Total subject	10	10	10
		Male	5	5	5
		Age	46.7±3.2		
B	SM	Total subject	20	20	20
		Male	12	12	12
		Age	5.6±2.2		
C	SM+GLU	Total subject	19	18	18
		Male	11	11	11
		Age	46.1±2.4		

SM: standard management (includes exercise, weight control, stretching of spine with specific traction/gravity exercise, defined hours of rest); BCP: *Boswellia/Centella* phytosome (500 mg tablets twice in a day); GLU: glucosamine (900 mg tablets twice in a day).

Ultrasound measurements

Posterior disk space

This measure was increased significantly more with BCP (P<0.05).

Disk density

It showed a significantly more decreased density with BCP (P<0.05) in comparison with the two control groups (the percent decrease indicating more hydration by the grey scale median). The Percent indicates the white (echogenic) percentage (GSM) in disk samples. The increase in hydration (due to expansion and increase in water content, decreases GSM). Black on ultrasound is the density of blood/water; white is the density of collagen. A disk becoming more expanded, perfused and hydrated becomes darker (more black components, more water inside).

Disk density data results indicate that the decrease in white (echogenic) percentage (on GSM) in disk samples. The increase in hydration (due to expansion and increase in water content, decreases GSM).

Black on ultrasound is corresponding to a lower density (the density of blood/water); on ultrasound white is the density of collagen tissue and tends to increase in fibrotic areas and scar tissues. A disk becoming more expanded, perfused and hydrated, generally becomes – on average – darker (with more black components, more water and more blood, sign of perfusion, inside).

Signs/symptoms

Signs/symptoms also were significantly more improved with the BCP (P<0.05) at 3 and 6 months in parallel with the TSL increase.

Also, general mobility improved (P<0.05) and rescue medications were needed less (P<0.05) with the BCP

Finally (Table II) the loss of working days due to pain and significant symptoms was significantly reduced with all managements (but significantly more than in the other two groups with BCP).

Discussion

In this registry study for the first time, the potential role of BCP, a new food-grade formulation of the association of highly standardized *Boswellia serrata* and *Centella asiatica* extracts, was demonstrated as a faster re-expansion of the intervertebral disks in symptomatic subjects with “flattened” disks in the lower spine, due to wrong posture

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The production of derivative works from the Article is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

TABLE II.—Clinical and physiological data.

Parameters	Group	Inclusion	3 months	6 months
Supine height	A	172.5; 4.2 cm	176.3; 13* +3.8	177.9; 2.2*
	B	172.6; 4.1	174.8; 3 +2.2	175; 2.3
	C	173.2; 3.1	174.8; 2.6 +1.7	174.3; 1.1
Total spine length (normal value: 569.4 mm; 17.6)	A	558.2; 4.1 mm	595.5; 2.8* +37.3	+41; 4*
	B	561.3; 4	580.3; 5.3 +19.3	+20; 1.8
	C	566; 5.2	586; 2.9 +20	+21; 2
Disk space ultrasound	A	5.6; 1.2	7.3; 0.8*	7.6; 1*
	B	5.4; 1	6; 0.9	6.2; 0.8
	C	5.2; 0.8	6.1; 0.6	6.3; 0.8
Signs/symptoms Score 0-4	A	3.2; 1.1	2; 1.2	1.5; 0.8*
	B	3.17; 1.7	2.8; 1.1	2.3; 0.2
	C	3.21; 0.2	2.7; 0.9	2.4; 0.6
Disk density % decrease indicates more hydration on grey scale median	A	65%	52	41.3*
	B	66%	58	57
	C	65.4%	55	54
Mobility Score 0-4	A	1.3; 0.2	3.3; 0.2*	3.5; 0.7*
	B			3; 0.3
	C			3.1; 0.4
Lost working Days	A	4.5; 0.4		3.3; 1.2/180 days*
	B	7.2; 0.2		5.7; 1/180 days
	C	6; 0.3		5; 1.5/180 days
Rescue medications Diclofenac, 50 mg cp/doses	A			6.8; 1*
	B			16.7; 2.2
	C			14; 0.9
Side effects	A		0	0
	B		0	0
	C		0	0
Tolerability	A		Very good	Very good
	B		Very good	Very good
	C		Very good	Very good

\*P<0.05

and compression after repeated trauma. BCP were associated to standard management including a specific exercise program and risk factors control resulting well tolerated with no observed adverse events during the 6-month supplementation.

Standard management, including specific elongation exercises, is generally effective in increasing the length of the spine and in increasing total height and in re-expanding the intervertebral disk structures and their hydration-perfusion. As shown by astronauts, in absence of gravity, height can be regained in absence of weight. Of two similar twins the one in space gained 12 cm in 6 months, mainly due to spinal elongation and disks re-expansion, in comparison with his twin who remained on the ground and using a comparable diet and exercise pattern. This was a subject >50 years.<sup>20</sup> The observations of P. Sager at the Bispebjerg Hospital in Copenhagen (Department of surgery M) suggest that the IVD may be re-expanded with appropriate exercise patterns, diet and with the help of pharmacological management.<sup>4</sup>

In this case BCP, the standardized combination of two botanical extracts formulated in a lecithin-based delivery system with food-grade technology, had proven a faster health recuperation taking the most of their single beneficial contribution. *Boswellia* can be considered useful to control inflammation and pain at the spinal and disk levels, considering its characteristic anti-inflammatory activity that is not associated (as for NSAIDs) with possible, rare but severe side effects,<sup>21</sup> related to the main active components, boswellic acids.<sup>6-8</sup> However, pharmacokinetics studies revealed low and an inefficient systemic absorption of boswellic acids in animals and human. In order to improve the bioavailability of *Boswellia*, a lecithin-based delivery form of standardized *Boswellia serrata* extracts (Casperome®, *Boswellia* Phytosome®) has been developed showing the optimization of boswellic acids delivery in healthy volunteers.<sup>22</sup> *Boswellia* Phytosome has proven to support in an efficient way the potential of *Boswellia* supplementation in anti-inflammatory nutrition, thus demonstrating to be useful for bowel related inflammatory responses<sup>23-26</sup> and to improve physical function in subjects with joint and tendon challenges.<sup>27-29</sup>

*Centella asiatica* produces a modulation of the collagen and the elastic components in several tissues under transformation or stress (theoretically also at the disk level). *Centella asiatica* is active in the prevention of excessive scar tissue, it may produce a more stable structure within atherosclerotic plaque, controlling collagen apposition and structure and it has several, other complex activities under evaluation.<sup>11, 30-35</sup> The most known active compounds of *Centella* are asiaticoside, madecassoside, asiatic acid and madecassic acid which promote the synthesis of collagen, regulate inflammation by normalizing the hyperproliferation of keratinocytes and can restore the



natural homeostasis of the epidermis.<sup>36</sup> Recently, a new formulation of *Centella* in phytosome, demonstrated to be able to improve bioavailability of these main active components, thus potentially affecting even the brain; indeed, it is employed for its cognitive properties as a brain tonic and for its ability to improve learning performance and memory.<sup>37</sup>

In this registry study, the benefits of the rationale association of the two botanicals in a single and more functional ingredient, demonstrated a general positive amelioration in quality of life improving motility and consequently reducing the rescue medications, lost working days, and signs or symptoms. On the other hand, glucosamine has been used in several arthrosis-link conditions but there is no real evidence of a specific activity onto the disk structure and onto the elongation of the spine in these patients, as confirmed in our registry.

### Conclusions

In conclusion, the relative effects of *Boswellia* associated with *Centella* in a single food-grade delivery system on spinal elongation, disk space and signs/symptoms appears to double the efficacy of SM also improving symptoms, much faster and better in comparison with SM and SM+glucosamine. The effects of BCP appear to be clear already in 3 months; results are persisting and improve at 6 months, without side effects and with a very good tolerability profile. Results of this pilot study suggest the opportunity of a larger evaluation involving a wider population.

### References

1. Porter RS, Kaplan JL. The Merck Manual of Diagnosis and therapy. Twelfth edition. Kenilworth, NJ: Merck, Sharp & Dohme Corp; 2018.
2. Busscher I, Ploegmakers JJ, Verkerke GJ, Veldhuizen AG. Comparative anatomical dimensions of the complete human and porcine spine. *Eur Spine J* 2010;19:1104–14.
3. Hong CH, Park JS, Jung KJ, Kim WJ. Measurement of the normal lumbar intervertebral disc space using magnetic resonance imaging. *Asian Spine J* 2010;4:1–6.
4. Sager P. Spondylosis Cervicalis. Copenhagen: Munsgaard; 1977.
5. Siddiqui MZ. *Boswellia serrata*, a potential antiinflammatory agent: an overview. *Indian J Pharm Sci* 2011;73:255–61.
6. Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. *Boswellia serrata*: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet* 2011;50:349–69.
7. Banno N, Akihisa T, Yasukawa K, Tokuda H, Tabata K, Nakamura Y, et al. Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri*. *J Ethnopharmacol* 2006;107:249–53.
8. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. *Curr Med Chem* 2006;13:3359–69.

9. Brinkhaus B, Lindner M, Schuppan D, Hahn EG. Chemical, pharmacological and clinical profile of the East Asian medical plant *Centella asiatica*. *Phytomedicine* 2000;7:427–48.
10. Coldren CD, Hashim P, Ali JM, Oh SK, Sinskey AJ, Rha C. Gene expression changes in the human fibroblast induced by *Centella asiatica* triterpenoids. *Planta Med* 2003;69:725–32.
11. Belcaro G, Maquart FX, Scoccianti M, Dugall M, Hosoi M, Cesarone MR, et al. TECA (Titrated Extract of *Centella Asiatica*): new microcirculatory, biomolecular, and vascular application in preventive and clinical medicine. A status paper. *Panminerva Med* 2011;53(Suppl 1):105–18.
12. Spinal compression management: Physiodata. Copenhagen: University thesis; 1778.
13. Belcaro G, Cornelli U, Dugall M, Luzzi R, Hosoi M, Ledda A, et al. Panel 2013. Supplements and green drugs studies: new rules 2013. *Angiology Online* 2012.
14. Belcaro G, Cornelli U, Ledda A, Hosoi M. Assessment of nutraceuticals and food supplements. *Panminerva Med* 2011;53(Suppl 1):I–II.
15. Belcaro G, Nicolaidis AN. Natural drugs in vascular medicine: new observations. *J Cardiovasc Pharmacol Ther* 2002;7(Suppl 1):S1.
16. Belcaro G, Nicolaidis AN. A new role for natural drugs in cardiovascular medicine. *Angiology* 2001;52(Suppl 2):S1.
17. Singh R, Wang O. Clinical trials in “emerging markets”: regulatory considerations and other factors. *Contemp Clin Trials* 2013;36:711–8.
18. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. *Ann Math Stat* 1947;18:50–60.
19. Bradford Hill A. Medical Statistics. London: Hodder and Stoughton; 1994.
20. Beall DP, Wilson GL, Bishop R, Tally W. VAST Clinical Trial: Safely Supplementing Tissue Lost to Degenerative Disc Disease. *Int J Spine Surg* 2020;14:239–53.
21. Efferth T, Oesch F. Anti-inflammatory and anti-cancer activities of frankincense: Targets, treatments and toxicities. *Semin Cancer Biol* 2020;S1044-579X(20)30034-1. [Epub ahead of print]
22. Riva A, Morazzoni P, Artaria C, Allegrini P, Meins J, Savio D, et al. A single-dose, randomized, cross-over, two-way, open-label study for comparing the absorption of boswellic acids and its lecithin formulation. *Phytomedicine* 2016;23:1375–82.
23. Gupta I, Parihar A, Malhotra P, Singh GB, Lütke R, Safayhi H, et al. Effects of *Boswellia serrata* gum resin in patients with ulcerative colitis. *Eur J Med Res* 1997;2:37–43.
24. Gupta I, Parihar A, Malhotra P, Gupta S, Lütke R, Safayhi H, et al. Effects of gum resin of *Boswellia serrata* in patients with chronic colitis. *Planta Med* 2001;67:391–5.
25. Khajuria A, Gupta A, Malik F, Singh S, Singh J, Gupta BD, et al. A new vaccine adjuvant (BOS 2000) a potent enhancer mixed Th1/Th2 immune responses in mice immunized with HBsAg. *Vaccine* 2007;25:4586–94.
26. Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R. [Therapy of active Crohn disease with *Boswellia serrata* extract H 15]. *Z Gastroenterol* 2001;39:11–7. [German.]
27. Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, et al. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. *Arthritis Res Ther* 2008;10:R85.
28. Franceschi F, Togni S, Belcaro G, Dugall M, Luzzi R, Ledda A, et al. A novel lecithin based delivery form of Boswellic acids (Casperome®) for the management of osteo-muscular pain: a registry study in young rugby players. *Eur Rev Med Pharmacol Sci* 2016;20:4156–61.
29. Feragalli B, Ippolito E, Dugall M, Cacchio M, Belcaro G, Cesarone MR, et al. Effectiveness of a novel boswellic acids delivery form (Casperome®) in the management of grade II ankle sprains due to sport trauma - a registry study. *Eur Rev Med Pharmacol Sci* 2017;21:4726–32.
30. Sharma S, Gupta R, Thakur SC. Attenuation of collagen induced arthritis by *Centella asiatica* methanol fraction via modulation of cytokines and oxidative stress. *Biomed Environ Sci* 2014;27:926–38.

31. Cotellesse R, Hu S, Belcaro G, Ledda A, Feragalli B, Dugall M, *et al.* Centella asiatica (Centellicum®) facilitates the regular healing of surgical scars in subjects at high risk of keloids. *Minerva Chir* 2018;73:151–6.
32. Belcaro G, Cornelli U. Variations in Echogenicity in Carotid and Femoral Atherosclerotic Plaques with Pycnogenol+Centella Asiatica Supplementation. *Int J Angiol* 2017;26:95–101.
33. Belcaro G, Dugall M, Ippolito E, Hosoi M, Cornelli U, Ledda A, *et al.* Pycnogenol® and Centella asiatica to prevent asymptomatic atherosclerosis progression in clinical events. *Minerva Cardioangiol* 2017;65:24–31.
34. Belcaro G, Ippolito E, Dugall M, Hosoi M, Cornelli U, Ledda A, *et al.* Pycnogenol® and Centella asiatica in the management of asymptomatic atherosclerosis progression. *Int Angiol* 2015;34:150–7.
35. Belcaro G, Dugall M, Hosoi M, Ippolito E, Cesarone M, Luzzi R, *et al.* Pycnogenol® and Centella Asiatica for asymptomatic atherosclerosis progression. *Int Angiol* 2014;33:20–6.
36. Segond C, Théron E, Petit V, Loiseau A. Innovative natural active ingredient with anti-inflammatory properties. *Antiaging Physiology to Formulation* 2006:189–196.
37. Sbrini G, Brivio P, Fumagalli M, Giavarini F, Caruso D, Racagni G, *et al.* Centella asiatica L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex. *Nutrients* 2020;12:355.

*Conflicts of interest.*—Antonella Riva, Giovanna Petrangolini and Stefano Togni are Indena's employees.

*Authors' contributions.*—All authors read and approved the final version of the manuscript.

*History.*—Article first published online: September 8, 2020. - Manuscript accepted: July 22, 2020. - Manuscript received: June 26, 2020.