

## Efficacy of solid lipid *Boswellia serrata* particles (SLBSP) in osteoarthritis of knee

Preeti Gota<sup>a\*</sup>, Neena Damle<sup>b</sup>, Sneha Patil<sup>c</sup>, Sumer Singh<sup>d</sup>, Mukesh Nandave<sup>e</sup>, Vikram Gota<sup>f</sup>, Lal Hingorani<sup>g</sup>

<sup>a</sup> School of Pharmacy and Medical Science, Singhania University, Jhunjhunu-333515, Rajasthan, India

<sup>b</sup> Department of Kaya Chikitsa, DY Patil University School of Ayurveda, Nerul, Navi Mumbai-400706, India

<sup>c</sup> Gahlot Institute of Pharmacy, Koprkhairane, Navi Mumbai-400709, India

<sup>d</sup> School of Life Sciences, Singhania University, Pacheri Bari, Jhunjhunu-333515, Rajasthan, India

<sup>e</sup> Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, Vile Parle, Mumbai-400056, India

<sup>f</sup> Department of Clinical Pharmacology, ACTREC, Tata Memorial Centre, Kharghar, Navi Mumbai-410210, India (g) Pharmanza Herbal Pvt. Ltd., PO Box # 4, Dharmaj-388430, Gujarat

### Abstract

Osteoarthritis of the knee (OA knee) is a chronic, progressive, skeletal, degenerative disorder often associated with restricted mobility and a poor quality of life. Non-steroidal antiinflammatory drugs (NSAIDs) are often employed in OA for symptomatic treatment of pain. Boswellic acids are known to have anti-inflammatory properties. We investigated the clinical utility of Solid Lipid *Boswellia serrata* Particles (SLBSP) for the symptomatic treatment of OA knee. It was a prospective, interventional, single-center clinical trial in patients with symptomatic OA knee. Subjects were treated with SLBSP capsules for two months. Improvement in pain and function was assessed with the help of Western Ontario and McMaster Universities OA index (WOMAC), Visual Analog Scale (VAS) and the need for rescue analgesics. The outcomes of interest at one month and two months were compared against baseline by one-way ANOVA. Twenty two patients were eligible for final analysis. Treatment with SLBSP resulted in marked improvement in pain and function scores. WOMAC score improved by 18.2% and 14.6% at 1 month and two months respectively ( $p < 0.05$ ). Similar change was observed in VAS score i.e., 19% and 26% improvement respectively during the same period ( $p < 0.05$ ). However, the most significant effect was observed in the need for rescue analgesics which reduced markedly by 67% during the first month and 76% in the 2 months compared to baseline ( $p < 0.01$ ). No adverse effects were observed due to treatment. Compliance to treatment was greater than 80% in all patients. SLBSP may be a safe and effective alternative to NSAIDs for symptomatic treatment of OA knee.

**Key words:** *Boswellia serrata*, Osteoarthritis of knee, WOMAC, VAS, Rescue analgesics

\* Corresponding Author

**Ms. Preeti Gota**

School of Pharmacy and Medical Sciences  
Singhania University

Pacheri Bari, Jhunjhunu-333515

Rajasthan, India

Ph: +91 7715019110, Email: preeti\_qa@yahoo.com

### INTRODUCTION

Osteoarthritis of the knee (OA knee) is a common, chronic, progressive, skeletal, degenerative disorder [1]. Despite continued physiotherapy and treatment with non-steroidal anti-inflammatory drugs (NSAIDs), the disease could be unremitting, eventually affecting the mobility of individuals and their quality of life.

This disorder is common in the elderly and is most often treated with NSAIDs or cyclooxygenase-2 (COX-2) inhibiting drugs and physiotherapy. NSAIDs block the synthesis of prostaglandins but do not block the other mediators of inflammation, namely leukotriene and the complement pathways. Chronic use may also lead to gastrointestinal and kidney complications [2]. Therefore, a better alternative for the treatment of osteoarthritis is needed, and a search is underway for a non-synthetic, natural drug derived from plant or herbal sources because historically, natural drugs have been shown to be better tolerated with reduced frequency of serious adverse drug reactions (ADRs).

The *Boswellia* species are trees located in India, Ethiopia, Somalia, and the Arabian Peninsula, and they produce a gum resin called olibanum, better known in the western world as frankincense. This resin possesses anti-inflammatory, anti-arthritic, and analgesic properties. *Boswellia* can inhibit the leukotriene biosynthesis in neutrophilic granulocytes by inhibiting 5-lipoxygenase (5-LOX), thus affecting various inflammatory diseases that are perpetuated by leukotrienes. Clinically, the substance is used in the treatment of degenerative and inflammatory joint disorders. It reduces the total white blood cell count in joint fluid, and it also inhibits leukocyte elastase, which is released in rheumatoid arthritis [3]. Its main chemical constituents are boswellic acids (BA) which are complex mixture of Pentacyclitriterpenic acids:  $\beta$ -boswellic acids, Acetyl- $\beta$ -boswellic acids, 11-Keto- $\beta$ -boswellic acids (KBA), Acetyl-11-Keto- $\beta$ -boswellic acids (AKBA) [4].

Preliminary pharmacokinetic studies revealed poor bioavailability, especially of KBA and AKBA. They are steroidal (lipophilic) in nature and do not solubilize in the intestinal fluid. Complexing of phospholipids with standardized botanical extracts has provided dramatic

enhancement of bioavailability and faster and improved absorption in the intestinal tract [5]. Recently, Sharma et al demonstrated improved ex-vivo absorption of the phospholipid complex of *Boswellia serrata* extract using everted goat small intestine sac [6]. Sterk et al have shown that bioavailability of BA increases when administered concomitantly with high fat diet in rats [7]. A human pharmacokinetic study of BA has shown small concentration of KBA and absence of AKBA in plasma when given empty stomach [8]. A solid lipidized Boswellic acid particles was therefore prepared to address the issue of low bioavailability of BA. The present study aims to investigate the clinical utility of Solid lipidized *Boswellia serrata* particles for the symptomatic treatment of OA knee.

## MATERIALS AND METHODS

Solid lipid *Boswellia serrata* particles (WokVida™) was procured from Pharmanza Herbal Pvt. Ltd. Capsules containing 333mg of the formula equivalent to 100 mg of 40% Boswellic acids by HPLC were used for study.

### Patients and setting

Patients with OA knee were enrolled for the study from DY Patil University School of Ayurveda, Navi Mumbai, from December 2013 to October 2014. Adult patients aged 18 years and above with symptomatic unilateral or bilateral osteoarthritis of the knee as defined by the American College of Rheumatology criteria were enrolled. Patients should have had at least moderate pain in the knee (rated at 40 or greater by the subject on a visual analogue scale) during the most painful knee movement during the last month requiring use of analgesic or anti-inflammatory agents for control of pain for at least seven days during the last month. Patients with baseline functional capacity grade 1 to 3, in which grade 1 is complete ability to carry out usual activities without handicap, grade 2 is ability to adequately conduct usual activities

despite handicap of discomfort or limited mobility of one or more joints, and grade 3 is limited ability to carry out usual activities (American Rheumatism Association functional class).

Patients with body mass index (BMI)  $\geq 35$  kg/m<sup>2</sup>, baseline functional grade 4 OA, inflammatory arthritis, gout, pseudogout, or Paget's disease, presence of chronic pain syndromes, such as fibromyalgia or reflex sympathetic dystrophy, that may interfere with the assessment of joint symptomatology, severe bursitis of the knee, history of acute joint trauma within 30 days of study entry, complete loss of articular cartilage, history of total knee replacement, taken intra-articular/intramuscular corticosteroids or intra-articular hyaluronan and hyalans within 30 days of study entry, severe renal dysfunction defined as a serum creatinine greater than 2 mg/dL, clinically significant liver disease (ALT/AST >2.5 times the upper limit of normal), unwillingness or inability to abstain from alcohol for the study duration, known hypersensitivity to Boswellia extracts or NSAIDs and pregnant or nursing women were excluded from the study.

### **Details of intervention and endpoints**

It was a prospective, interventional, single-center clinical trial in patients with symptomatic OA knee. The primary endpoint of the study included improvement in patient reported outcomes – Western Ontario and McMaster Universities OA index (WOMAC) and Visual Analog Scale (VAS). WOMAC is widely used in the evaluation of Hip and Knee Osteoarthritis. It is a self-administered questionnaire consisting of 24 items divided into 3 subscales: Pain, stiffness and physical function. The test questions are scored on a scale of 0-10, depending on the severity. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations [9,10].

A co-primary endpoint was the reduction in the need for rescue analgesics during the course of treatment. These parameters were recorded at baseline (before the start of treatment) and at 1 month and 2 months after initiating treatment with SLBSP.

Patients were enrolled on the study after obtaining a written informed consent. A pre-study washout of seven days was given. After washout, baseline pain and function assessment was done by WOMAC scale, VAS and antero-posterior radiographs of affected knee joint in full extension. The number of occasions on which rescue medications (analgesics) were consumed in the 30 days prior to enrollment in this study was also documented. The study patients were treated with WokVida<sup>TM</sup>, one capsule to be taken 3 times daily for the duration of two months.

### **Visit and Assessment Schedule**

Before the start of study, baseline evaluation comprising of complete blood counts (CBC), Liver function test (LFT), Renal function test (RFT), Electrocardiogram (ECG) and Urine analysis were carried out for each patient at DY Patil University School of Ayurveda, Navi Mumbai. Eligible patients were issued the drug for 30 days and asked to return to the clinic for a refill for the second month. Patients were asked to make an entry in a 'Subject Dairy' every time the drug was consumed, and write down the reason for every missed dose. Capsule count was taken at every visit to record compliance to treatment. All subjects underwent physiotherapy as recommended. Inter-current illness and Adverse Events (AEs), if any, were captured during each visit. Breakthrough arthritic pain was treated with NSAIDs / other agents as per standard practice. At the end of two months of treatment, patients were called to the OPD for the final visit. Capsule count, WOMAC score, VAS score, Rescue medication use were

documented during this visit. Safety evaluation comprising of clinical assessment, CBC, LFT, RFT, urine analysis and ECG was also carried out during this visit in addition to X-ray of the affected knee.

### Statistical Considerations

Data was analyzed descriptively. One-way Analysis of Variance (ANOVA) with level of alpha set at 0.05 was used to compare WOMAC, VAS scores and rescue analgesics at baseline, one month and two months.

### Ethical Considerations

The protocol was approved by the Institutional Ethics Committee of DY Patil University School of Ayurveda, Navi Mumbai. The study was conducted in accordance with the GCP principles stated in the Declaration of Helsinki.

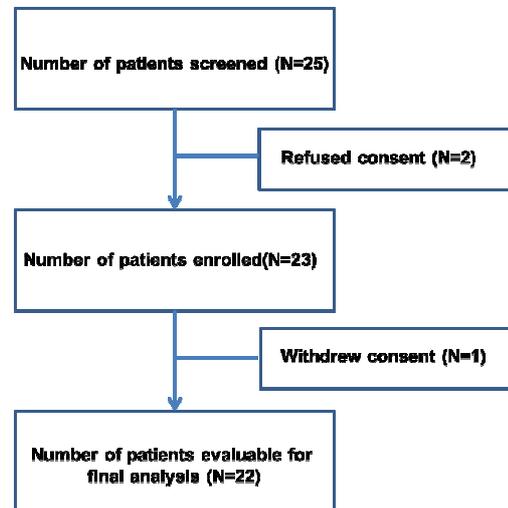
## RESULTS

### Study population

Twenty five patients of osteoarthritis of the knee were screened and 23 were enrolled on the study. One patient withdrew consent in the first month of treatment citing inability to come for scheduled visits and hence was not evaluable for primary outcome. Details regarding number of patients screened, enrolled and eligible for final analysis are shown in figure 1. The median age of the patients was 58 years (Table 1).

**Table 1. Patient demographics**

Demographic characteristics	N=22
Age (years) Median (Range)	58 (35-81)
Sex	
Male	5
Female	17
Baseline WOMAC Mean±SD	6.4±0.97
Baseline VAS Mean±SD	6.0±1.93
Baseline rescue medicines Mean±SD	10.3±2.70



*Figure 1: CONSORT flowchart*

### Efficacy

#### i) WOMAC Score:

An improvement was observed in WOMAC score as a function of time. The percentage improvement in WOMAC score was found to be 18.2% and 14.6% at one month and two months respectively (Figure 2a). The overall improvement at two months compared to baseline was 30%. The improvement in WOMAC score at the end of one month and two months was statistically significant compared to baseline ( $P < 0.05$ ).

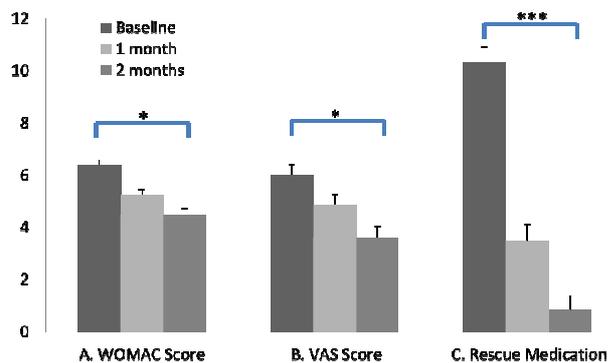


Figure 2: Outcome assessment WOMAC (2a) and VAS (2b) scores at baseline and at one month and two months after initiating treatment with SLBSP. The use of rescue medications before and during the course of treatment is also shown (2c). \*  $p < 0.05$ , \*\*\*  $p < 0.01$ .

ii) VAS Score:

Similar improvement was also observed in VAS score over the two months of treatment. There was a marked decrease in the VAS from baseline to first month (19%) and from first month to second month (26%). The overall decrease in the VAS score from baseline to second month was 40% (Figure 2b). The improvement in VAS score at the end of one month and two months was statistically significant compared to baseline ( $P < 0.05$ ).

iii) Rescue medication:

Improvement in symptom scores resulted in a corresponding decrease in the use of rescue analgesics. This is a direct and objective marker of the utility of therapeutic interventions in osteoarthritis. Dependency on rescue analgesics for breakthrough pain reduced by 67% in the first month and a further 76% in the second month for a overall reduction of 92% at two months compared to baseline (Figure 2c). The difference was statistically significant ( $P < 0.01$ ) compared to baseline. Interestingly, none of the patients had any sort of improvement in the radiological appearance of OA nor was any progression documented.

**Compliance and adverse effects**

No adverse events were observed during the study. Information collected from the subject diary as well as the capsule count showed extremely high compliance to treatment with more than 80% compliance observed in all patients [Median(range) = 92% (86-100%)]. The high compliance rate is an indirect measure of the safety and efficacy of the investigational product.

**DISCUSSION**

SLBSP markedly improved the symptoms of OA knee while not modifying the disease itself. A notable finding was the significant reduction in the need for rescue analgesics during the course of treatment with SLBSP. This is an important advantage because prolonged use of NSAIDs is associated with deleterious effects on the kidneys and heart. Historically, drugs of herbal origin are generally well tolerated and not surprisingly, we did not observe any side effects due to SLBSP during the two months of treatment.

Boswellic acids, KBA and AKBA, are known to have anti-inflammatory properties. However, their clinical efficacy is limited by poor oral bioavailability [5,6]. Several authors in the past have investigated the pharmacokinetics and efficacy of plain uncomplexed BSE [8,11,12,13,14]. This is the first study where the SLBSP has been shown to be effective for symptomatic relief of OA knee. In fact, the marked relief from symptoms prompted many patients to continue treatment long after the trial was completed. In spite of its ability to offer symptomatic relief, SLBSP did not have any influence on the radiographical features of OA. At the same time, none of the patients had radiological progression of OA either during the course of treatment. It is not clear whether SLBSP works only as an anti-inflammatory agent or has ability to modify the course of the

disease. Future studies should focus on the mechanism of action of boswellic acids using suitable models of osteoarthritis to understand if mechanisms other than anti-inflammatory effects are responsible for its biological actions.

The study has several important clinical implications. First of all, SLBSP's ability to reduce dependency on NSAIDs is particularly beneficial for elderly patients who generally have some extent of renal impairment due to advancing age. Secondly, the drug was very well tolerated and did not result in any adverse clinical or laboratory findings including renal and hepatic function. However, compliance to treatment may be a potential limitation because the drug has to be consumed three times a day. We observed that the median compliance was more than 90% with vast majority of patients not missing a single dose. However, compliance in a clinical trial setting is generally better than routine hospital practice, and therefore a need for extended release formulations may be felt once the drug is used routinely in the clinics.

The study has some limitations. Because of the short duration of the trial, long term effects of the drug on the disease could not be investigated. It will be interesting to study the effect of the drug on radiological and clinical progression of OA after prolonged administration. Also, such a study will help us to understand the long-term safety and tolerability of SLBSP. Future studies should focus on these end points in a larger set of patients.

To conclude, SLBSP may be a safe and effective treatment for the symptomatic control OA knee. It caused significant improvement in the WOMAC and VAS scores and the need for rescue medication. These findings may have major implications in elderly patients with OA knee.

**CONFLICT OF INTEREST** – Dr. Lal Hingorani is the managing director of

Pharmanza Herbal Pvt. Ltd. which manufactures and markets WokVida™.

## REFERENCES

1. N. Kimmatkar, V. Thawani, L. Hingorani, R. Khiyani. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee – A randomized double blind placebo controlled trial. *Phytomedicine* 10, (2003), pp. 3–7.
2. J. Claria. Cyclooxygenase-2 Biology. *Current Pharmaceutical Design*. 9 (2003), pp. 2177-2190.
3. J. Maroon, W. Bost, A. Maroon. Natural anti-inflammatory agents for pain relief. *Surg Neurol Int.* 1, (2010), pp. 80.
4. A. Rahman, H. Naz, T. Makhmoor, et al. Bioactive Constituents from *Boswellia papyrifera*. *J. Nat. Prod.* 68, (2005), pp. 189-193.
5. P. Kruger, R. Daneshfar, G. Eckert, et al. Metabolism of Boswellic acids in vitro and in vivo. *Drug Metab Dispos.* 36, (2008), pp. 1135-42.
6. A. Sharma, N. Gupta, and V. Dixit. Complexation with phosphatidyl choline as a strategy for absorption enhancement of boswellic acid. *Drug Delivery* 17, (2010), pp. 587–595.
7. V Sterk, B Büchele, T Simmet. Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. *Planta Med.*70, (2004), pp. 1155-60.
8. S. Sharma, V Thawani, L Hingorani, M Shrivastava, V R Bhate, R Khiyani. Pharmacokinetic study of 11-keto  $\beta$ -Boswellic acid. *Phytomedicine* 11, (2004), pp. 255-260.
9. American College of Rheumatology. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) <http://www.rheumatology.org/practice/clinic>

al/clinicianresearchers/outcomes-instrumentation/WOMAC.asp. (accessed 12 July 2013).

10. WOMAC Osteoarthritis Index. <http://www.womac.org/womac/index.htm>. (accessed 12 July 2013).
11. S. Sontakke, V. Thawani, S. Pimpalkhute, P. Kabra, S. Babhulkar, L. Hingorani. Open, Randomized, controlled clinical trial of *Boswellia serrata* extract as compared to valdecoxib in osteoarthritis of Knee, *Indian J Pharmacol.* 39, (2007), pp. 27-29.
12. S. Shah, I. Rathod, B. Suhagia, et al. Estimation of boswellic acids from market formulations of *Boswellia serrata* extract and 11-keto b-boswellic acid in human plasma by high-performance thin-layer chromatography. *Journal of Chromatography B* 848, (2007), pp. 232–238.
13. R. Kulkarni, P. Patki, P. Jog, G. Gandage, B. Patwardhan, Treatment of osteoarthritis with a herbomineral formulation: A double-blind, placebo- controlled, cross-over study. *J Ethnopharmacol.* 33, (1991), pp. 91-95.
14. M. Abdel-Tawab, O. Werz, M. Schubert-Zsilavec. *Boswellia serrata*: An Overall Assessment of In Vitro, Preclinical, Pharmacokinetic and Clinical Data. *Clin Pharmacokinet.* 50, (2011), pp. 349-69.