

Boswellia Derivates and Rehabilitation Program in Knee Osteoarthritis Patients

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In the present study, we aim to highlight the role of Boswellia derivates in the rehabilitation of the clinical and functional status of patients with knee osteoarthritis. Probably, the judiciously association between herbal products and rehabilitation methods (ultrasound and physical exercise) will give the optimal healthcare for this type of patients.

Keywords: knee osteoarthritis, Boswellia derivates, rehabilitation program

Osteoarthritis (OA), a painful chronic disease affecting the joint cartilage, subchondral bone, joint capsule and synovial, is one of the most common causes of physical disability [1]. The joint most commonly affected by OA is the knee - one of the pivots of the lower driveline with human specific purpose, orthostatic posture and walking. Knee OA is a major social and health problem and a cause of disability among the aging population [2, 3].

OA has a multifactorial aetiology and is characterized by a disrupted state of physical and mental wellbeing of the patient. Its pathogenesis includes mechano-transduction, the interplay between metalloproteases (MMP3, MMP13), protease inhibitors and cytokines on cartilage degradation and mechanisms of cartilage repair [2, 4]. Cytokines (especially interleukin-1 and tumour necrosis factor α) can promote articular cartilage extracellular matrix protein degradation or synergize with other cytokines to amplify and accelerate cartilage destruction [4, 5]. Recently, other cytokines were also identified as being involved in the progressive breakdown of articular cartilage. Transcription factor hypoxia-inducible factor-2 α (HIF-2 α), which is highly enhanced in OA cartilage, has been shown to activate catabolic metalloproteinases (MMP) including MMP-13 and promote chondrocyte apoptosis [6, 7]. Anabolic cytokines, including transforming growth factor-beta (TGF- β), insulin-like growth factor-1 (IGF-1), and fibroblast growth factor-2 (FGF-2), have been characterized as potential chondroprotective agents [5].

Medical care of patients with osteoarthritis is provided by a multidisciplinary team and may be challenging because of the presence of co-morbidities that coexist with OA. The Technical Expert Panel of revised ACR guidelines strongly recommends that all patients with symptomatic knee OA be enrolled in an exercise program and the use of topical rather than oral NSAIDs [6]. Long term use of NSAIDs has been found to associate with enhanced risk for gastrointestinal bleeding, hypertension, congestive heart failure and renal insufficiency, among other adverse effects, so effective and safer alternative treatments for OA are

urgently needed [9-11]. In the last decades, it was mentioned in medical literature the herbal care for OA patients. This type of treatment is in accordance with actual mentioned challenges in treating OA, especially in elderly patients [12].

One type of Boswellia derivates are manufactured by Himalaya Herbals a company based in India, endorsed by doctors worldwide and used by customers in over 60 countries. This herbal product made up of several indigenous plants which are well known in Indian medicine is used in osteoarthritis patient in two forms - topical and tablet, since forty years ago [13,14].

Experimental part

Hypothesis

In the present study, we aim to highlight the role of Boswellia derivates tablets in the rehabilitation of the clinical and functional status of patients with knee OA. Probably, the judiciously association between herbal products and rehabilitation methods (ultrasound and physical exercise) will give the optimal healthcare for this type of patients.

Patients and methods

We conducted our observational study during the period May 2017 - November 2017 in the Rehabilitation Department of the Filantropia Hospital Craiova. Our research was performed on 70 patients, all diagnosed with knee osteoarthritis. The study was approved by the institutional ethics review committee. The inclusion criteria taken into account were: patients diagnosed with primitive osteoarthritis according to the American College of Rheumatology, criteria also accepted in our country; at least 15 years of disease progression; painful knee for a period of 48 h after physical activity; absence of knee injuries at least 6 months before; compliance with physical exercise during the healthcare program.

We completed an initial etiopathogenic, clinical, laboratory (laboratory screening, imaging examination - radiography and ultrasound for evidencing joint effusion

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and synovial reaction) and functional assessment. For a functional assessment, we used:

- the VAS - Visual Analogue Scale (0 = absence of pain and 10 = maximum pain score),

- the WOMAC scale to assess the impact of disease in performing activities of daily living (0 = maximum functional status and 96 = minimum, with maximum disruption of daily activities),

- the Lequesne Functional Index to assess the effectiveness of therapeutic interventions (total index 0 = none disability, 1 - 4 = mild disability, 5 - 7 = moderate disability, 8 - 10 = severe disability, 11 - 13 = very severe disability and ≥ 14 extremely severe disability).

Evaluation of patients was carried out in three stages - initial (T1), after 3 months (T2) - during which an in-hospital program of rehabilitation was conducted, and after a further 3 months (T3) in an outpatient setting. The healthcare objectives were: painful status control; controlling the inflammatory process; regaining stability and mobility of the knee and keeping the knee functional in the biomechanical structure of the limb; correcting the abnormal walking scheme, with recovery of normal walking; regaining motor control, optimal knee function; maintain the quality life of patient.

The rehabilitation program was complex, based on non-surgical measures and included:

- non-pharmacological measures - educational, dietary and hygienic, posture, physical therapy massage and kinetic measures;

- pharmacological measures - Boswellia derivatives (Rumalaya Forte) / 2 tablets per day were given for 3 months period.

Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for processing the data. Data was recorded using Microsoft Excel files, then it was statistically analyzed to find relationship between clinical and laboratory parameters of patients. We used Z test for proportions to investigate the statistical significance of the difference between the frequency f of binary variables in general

population and the observed frequency p in our sample group. Because the study involved numerical comparisons between 3 sets of data from the same patients, recorded during 3 different visits, that did not have normal (Gaussian) distributions, we used the median, quartiles and minimum-maximum to describe the numerical data, and the nonparametric Friedman test, followed by post-hoc comparisons to detect significant differences between pairs of groups. To test the relationships between changes in the analyzed parameters we used Spearman's correlation coefficient.

Results and discussions

This is the first clinical study in Romania to evaluate the efficacy of one type of Boswellia derivatives in knee OA patients. Our study confirms the antiarthritic activity of this herbal product, where Boswellia serrata, Commiphora wightii and Glycyrrhiza glabra act synergistically, to reduce inflammation and pain. None of our patients reported any serious adverse effects during the study period of 6 months. There was no alteration in the laboratory parameters in patients on Boswellia derivatives. The weakness of our study is the lack of a control group to receive placebo, a difficult aspect in rehabilitation medicine. For the study pathology, there is a great difference between the prevalence in women and men - the percentages for the study group compared to the general population distribution in Romania hold a highly significant difference (Z test $p < 0.001$), as there are 51.4% women and 48.6% men in Romania. The differences concerning the area of residence are not significant (Z test $p = 0.503$) - Romania's distribution is 54% urban, 46% rural (table 1).

Comparing the values recorded for the flexion angle among the three visits (table 2), we observe a steady increase in the values, the overall differences being highly significant (Friedman $p < 0.001$). Performing post-hoc analysis, we found the values from the second visit to be greater than the initial values, and the values from the last visit being significantly greater than the intermediate values (fig. 1).

Analyzing the visual-analog scale recordings (fig. 2), we found highly significant differences among the three visits,

Table 1
CHARACTERISTICS OF THE STUDIED PATIENTS

Biographic data						Total
Gender	57 Women = 81.43%		13 Men = 18.57%			70
Residence	35 Urban = 50%		35 Rural = 50%			70
Age	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	70
	3p. = 4.29%	14 p. = 20.00%	30p. = 42.86%	20p. = 28.57%	3p. = 4.29%	100.00%
Parameters			T1 = 1st visit	T2 = 2nd visit	T3 = 3rd visit	
VAS			7.63 \pm 1.3	5.21 \pm 1.24	3.57 \pm 1.23	
WOMAC Scale			55.07 \pm 10.49	44.80 \pm 11.18	35.99 \pm 10.21	
Lequesne functional index			14.81 \pm 3.59	11.77 \pm 2.72	8.89 \pm 2.57	

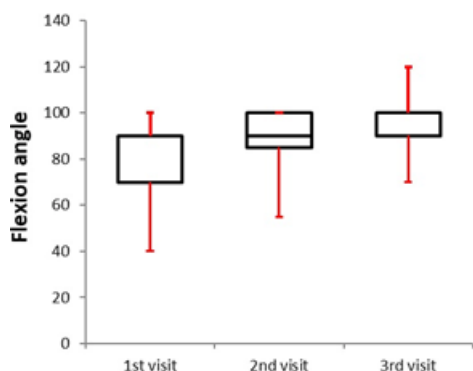


Fig. 1. Comparison of flexion angle values among the three visits

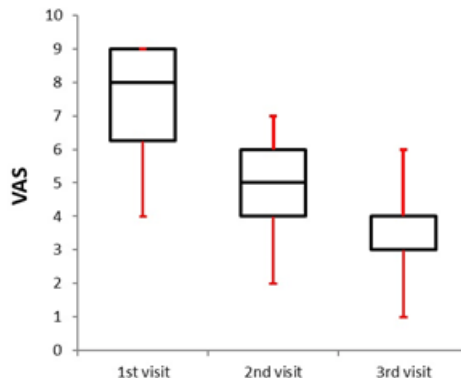


Fig. 2. Comparison of VAS values among the three visits

the values decreasing over time (Friedman $p < 0.001$); the post-hoc analysis showed the values from the first visit being lesser than the values from the second visit, which were significantly lesser than the values from the third visit.

The finding for the WOMAC scale values (fig. 3) and the Lequesne functional index values (fig. 4) are similar to those for VAS, showing a highly significant decrease over time (Friedman $p < 0.001$) (table 2).

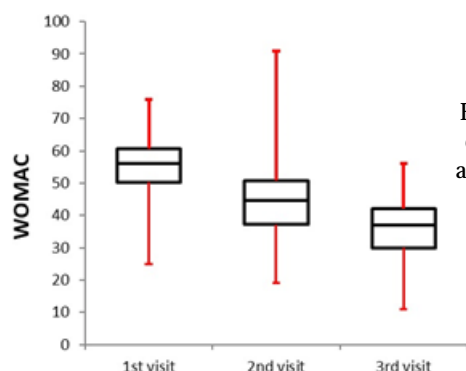


Fig. 3. Comparison of WOMAC values among the three visits

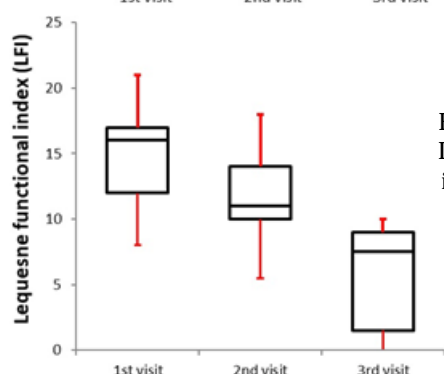


Fig. 4. Comparison of Lequesne functional index values among the three visits

Analyzing the correlation (table 2) between the increase in flexion angle and decrease of the perceived pain or discomfort in performing day to day functions, using Spearman's rho correlation coefficient, we found Lequesne functional index to show the greatest correlation to flexion angle ($\rho = -0.388$) (fig. 5), followed by WOMAC scale ($\rho = -0.308$) (fig. 6) and VAS ($\rho = -0.273$) (fig. 7).

Reviewing the literature shows that there are numerous clinical benefits of treatment with Boswellia derivatives in knee OA patients, without age limits and supervised rehabilitation program. Our observational study was performed taking into consideration an association between natural treatment and rehabilitation program. This

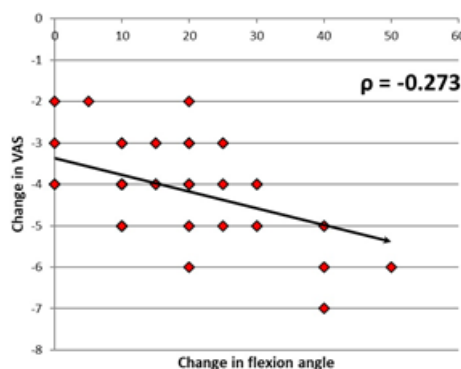


Fig. 5. Correlation between flexion angle changes and VAS changes during the study

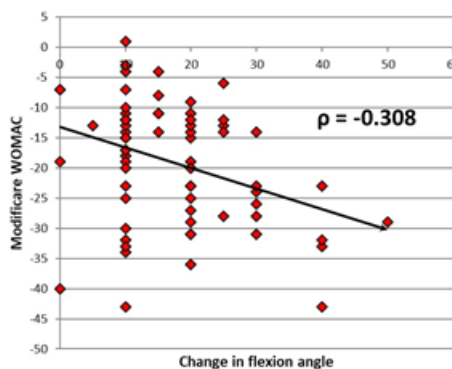


Fig. 6. Correlation between flexion angle changes and WOMAC changes during the study

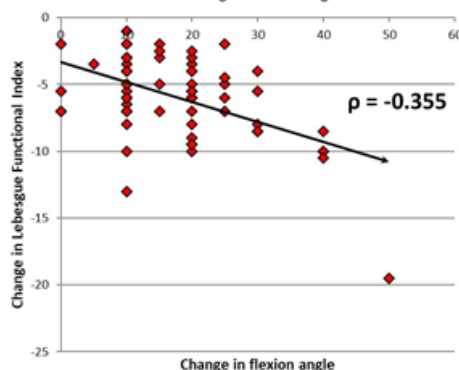


Fig. 7. Correlation between flexion angle changes and LFI changes during the study

herbal product shows significant improvement of symptoms like pain, swelling, joint malfunction and mobility in patients of OA and does not produce any serious side effects. Since the patients have frequent acute exacerbations of chronic osteoarthritis at frequent intervals, it requires symptomatic treatment from time-time. Although, it has no toxic effect [14].

Variable	Flexion angle			VAS		
Parameter	T1	T2	T3	T1	T2	T3
Minimum	40	55	70	4	2	1
1st Quartile	70	85	90	6.25	4	3
Median	90	90	100	8	5	4
3rd Quartile	90	100	100	9	6	4
Maximum	100	100	120	9	7	6
Variable	WOMAC			Lequesne functional index		
Parameter	T1	T2	T3	T1	T2	T3
Minimum	25	19	11	8	5.5	1.5
1st Quartile	50.25	37.25	30	12	10	7.5
Median	56	44.5	37	16	11	9
3rd Quartile	60.75	50.75	42	17	14	10
Maximum	76	91	56	21	18	16.5

Table 2
MEDIAN AND SPREAD INDICATORS FOR THE STUDY VARIABLES

Also the combination of herbal compounds of this type of *Boswellia* derivatives was different upon time, all combinations and herbal plants claimed to have analgesic and anti-inflammatory actions, besides antispasmodic activity and antiseptic action. Some constituents stimulate uric acid excretion; prevent gouty arthritis, osteoporosis and degenerative changes in the joints [15]. Clinical efficacy of herbal product - an Ayurvedic preparation is comparable to that of the commonly used drugs - Diclofenac sodium and Ibuprofen. The analgesic effect of *Boswellia* derivatives is comparable to that of Diclofenac and Ibuprofen [15, 16]. The combination of several herbs that compound our studied natural product is changing in time.

Today it is from the renowned Himalaya Herbals products have been researched clinically and standardized to guarantee bioequivalence. Himalaya Herbal Healthcare uses chromatographic fingerprinting, one of the most sophisticated standardization techniques, to ensure consistent quality and performance [17]. For the last two decades, formulation of studied product contains six herbal extracts as active ingredients: *Alpinia Galanga* (Rasna) 70 mg, *Boswellia Serrata* (*Boswellia* / *Shallaki*) 240 mg, *Commiphora Wightii* (Indian *Bedellium* / *Guggul*) 200 mg, *Glycyrrhiza Glabra* (Licorice / *Yashti madhu*) 70 mg, *Tinospora Cordifolia* (*Tinospora Gulancha* / *Guduchi*) 60 mg and *Tribulus Terrestris* (Small caltrops / *Gokshura*) 60 mg, like in our study. These ingredients have shown to have anti-inflammatory, anti-arthritis, immunomodulatory, muscle relaxant and analgesic activities [18]. This type of *Boswellia* derivatives tablets seem to be safe and effective drugs for treatment of OA-patients [19].

No side effects were reported by any of the patients [20].

Boswellia serrata is the primary and the most important constituent of studied natural product, which has been historically used in the treatment of OA. *Boswellia serrata* gum resin extract (BSE) containing boswellic acids (BAs) as the main bioactive principles. 3-O-acetyl-11-keto-betaboswellic acid (AKBA) is the most active component. These extracts have demonstrated their anti-inflammatory role, with good management of musculoskeletal pain and inflammation, due to several mechanisms of action including inhibition of inflammatory mediators, prevention of decreased glycosaminoglycan synthesis, improved blood supply to joint tissues [10, 21, 22].

All these medicinal plants may inhibit inflammatory mediators and interact with various cytokines, at least under experimental conditions. The mechanism of action of the oral herbal medicines is likely to be broader than that of non-steroidal anti-inflammatory drugs [23-27]. Although their mechanisms of action have not yet been elucidated in full detail, interactions with mediators of inflammation and cartilage destruction provide a rationale for using them to treat OA complaints. The active principle of a medicinal plant product is the sum of all ingredients that produce the medicinal action. Despite their advantages, herbal treatments in general, and studied tablet in special, raise several concerns, such as drug-herbal interactions, low bioavailability, insufficient regulatory guidelines at national and international levels [28].

Conclusions

Taken daily, this type of *Boswellia* derivatives product - a real natural product, without side effects - has demonstrated positive results in relieving pain due to osteoarthritis, promoting normal strength and flexibility of

muscle, with enhancing the quality of life in patients with knee OA.

Physiotherapy in association with studied herbal product represents the best *drug* for elderly patients with osteoarthritis, with a favorable impact on the whole body and wellbeing.

In the next years, the controlled studies may be conducted to evaluate the complex role of various *Boswellia* derivatives in the complete management of OA patient.

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