ORIGINAL ARTICLE

THE ROLE OF HERBAL EXTRACTS IN KNEE OSTEOARTHRITIS FEMALES REHABILITATION

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Abstract

In our observational study, we intend to set off the importance of an herbal complex based on *Boswellia serrata* in the rehabilitation of the complete status of females with knee osteoarthritis. An association between herbal extracts and rehabilitation methods will give the ideal healthcare for these patients.

Rezumat

Studiul observațional a urmărit rolul asocierii unui preparat din plante, bazat pe *Boswellia serrata*, în programul de reabilitare și controlul statusului clinic-funcțional al femeilor cu gonartroză primară. Asocierea judicioasă dintre produsele naturale și metodele de reabilitare (kinetoterapie) conferă soluția ideală pentru o calitate optimă a vieții pacientelor.

Keywords: knee osteoarthritis, herbal product, rehabilitation program

Introduction

Osteoarthritis (OA), a painful chronic disorder involving all components of synovial joint, represents one of the most frequent causes of physical disability [13]; according to the World Health Organization, OA is on the top ten disabling chronic disorders in developed states [15, 23, 31]. The joint most ordinarily interested by OA is the knee (knee OA - KOA - constitutes 83% of the global disease burden for OA) - the middle pivot of the lower limb with biomechanical role in walking and orthostatic posture [17]. Older age and female gender are two of the risk factors significantly associated with the onset of KOA, in accordance with the literature data [28]. Serious pain, a trademark symptom of KOA, affects activities of daily living [32] and is a leading risk factor for enhanced fall risk with major dysfunctional impact on the body [33].

OA has a multifactorial aetiology [35] and its pathogenesis involve mechano-transduction, the interaction between protease inhibitors, metalloproteases (MMP13, MMP3) and cytokines on cartilage change and mechanisms of its sole. Cytokines including tumour necrosis factor α (TNFα) and interleukin-1 (IL-1) - probably the foremost cytokines for cartilage deterioration, other cytokines (members of the IL-6 protein super family, IL-7, IL-17, IL-18) can elevate joint cartilage extracellular matrix protein abasement or action with other cytokines, to intensify and speed this process [2, 19]. In the last decade, former cytokines were also known as being implicated in the progressive degradation of joint cartilage tissue. Catabolic metallo-proteinases (MMP) are activated by the factor hypoxia-inducible factor-2α (HIF-2α) transcription, a complex process which is involved significantly in chondrocyte apoptosis and OA cartilage. Anabolic cytokines, including insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), and transforming growth factor-beta (TGF-β), have been qualified as possible chondroprotective factors [19]. Monocytes promote the synovitis process and disorder pathogenesis. These cells generate high levels of IL-1β and TNF compared to healthy persons [18].

Medical care in osteoarthritis is provided by a multi-disciplinary team and may be challenging because of the co-morbidities that coincide with OA [11]. In the last years, it was mentioned in the medical literature the major role of herbal care for OA patients. This type of treatment is in accordance with actual mentioned challenges in treating OA (limited potency of present

therapies, contraindications to management because of other disorders, lack of access or availability to treatments, difficulties with patients adhering to treatments) [11]. A phytotherapeutical Indian complex is administered to OA patient in two forms - topical and tablet, since forty years ago [30]. These tablets and creams are reported to be beneficial on the whole complex of complaints associated with OA disorders and are completely non-toxic. They are slow acting and need long-term therapy [5]. The combination of several herbs in the tablet is changing in time. Today, the formulation contains six herbal extracts as active ingredients: *Alpinia galanga* 70 mg, *Boswellia serrata* 240 mg, *Commiphora wightii* 200 mg, *Glycyrrhiza glabra* 70 mg, *Tinospora cordifolia* 60 mg and *Tribulus terrestris* 60 mg [7]. The phytocomplex contains: saponin triterpenes, flavonoids and other components such as amino acids, coumarins, tannins, sugars, starch, phyto-sterols and choline. This herbal complex improves the patient's condition through an anti-inflammatory activity, by suppressing the cyclo-oxygenase activity and prostaglandin formation, retarding the platelet aggregation, enhancing the antioxidant activity and scavenging the free radicals, inhibiting the expression of pro-inflammatory cytokines. It modulates the metabolic profile by promoting insulin secretion, by inhibiting gluconeogenesis and glycogenolysis, lowering the cholesterol-induced hyperlipidaemia and decreasing the hepatic steroid production. It stimulates the growth of bone forming cells, modifies the protein inside the bacterial cell wall, decreases the activity of tyrosinase, and the serum transaminase levels. It also possesses acetyl-cholinesterase inhibitory effects, enhances the levels of cerebral dopamine and the specific immune responses [11, 34, 37-39].

In our observational study, we intend to set off the importance of the phytocomplex based on *Boswellia serrata*, tablets and topical formulation, in the rehabilitation of the complex status of female patients with KOA. The association between herbal products and rehabilitation methods will give the optimal healthcare for KOA patients.

Materials and Methods

Study design. The research was performed on 57 females; all diagnosed with KOA, during the period May 2017 - November 2017 in the Rehabilitation Department of the "Filantropia" Hospital Craiova, Romania. Our study was authorized by the ethics review hospital board and a signed informed consent from all the subjects was registered. We completed initial etiopathogenic, clinical (flexion angle of the knee), laboratory (laboratory tests, knee X-ray and knee ultrasound) and functional evaluations using the VAS - Visual Analogue Scale for pain, the WOMAC scale to assess the impact in performing activities of daily living, the Lequesne Index to assess the effectiveness of therapeutic interventions.

Assessment of our patients was performed in three periods - first (T1), after 3 months (T2) - during which an in-hospital rehabilitation was carried on, and after a further 3 months (T3) in an outpatient evaluation. The rehabilitation objectives were: knee aching control; managing the inflammatory process; recovering motor control, optimal knee function and maintain the quality life of patients. The rehabilitation program was complex, based on non-surgical measures and comprised: non-pharmacological aspects - educational, dietary and hygienic, posture, physical (electrotherapy - TENS, ultra-sound, magnetodiaflux, and thermotherapy - paraffin), massage and kinetic exercises; pharmacological measures - herbal complex based on *Boswellia serrata*, 2 tablets *per* day, were given for 3 months.

Statistical analysis was carried out using the following: Microsoft Excel (Microsoft Corp., Redmond, WA, USA), XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for refining the data. We used Z test for quotients, to analyse the statistical significance of the difference between the frequency f of binary variables in general population and the determined frequency p in our representative 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 see significant differences between patients.

Results and Discussion

Our study group consisted in 57 women, aged 41 to 82 (Table I) and the differences concerning the area of residence were not significant (Z test $p = 0.836$) with 54% urban, 46% rural. The age distribution shows a slight asymmetry towards older ages. The weight analysis showed a great asymmetry towards a higher body mass index (BMI), only 8.57% of patients being normoponderal.

Table I

Characteristics of the studied patients

Biographic data						Total
Residence	30 patients Urban = 52.63%			27 patients Rural = 47.37%		57 patients
Age	40 - 49 years	50-59 years	60 - 69 years	70 - 79 years	80 - 89 years	
	5.26%	21.05%	42.11%	26.32%	5.26%	100%
Weight	Normal	Overweight	Obese I	Obese II	Obese III	
	7.02%	40.35%	31.58%	17.54%	3.51%	100%

Comparing the values recorded for the flexion angle among the three visits (Table II), we observed a steady increase in the values, the overall differences being highly significant (Friedman, $p < 0.001$) (Figure 1). 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 higher than the intermediate values. Analysing the visual-analogue scale recordings, we found highly significant differences 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 lower than the values form the second visit, which were significantly lower than the values from the third visit (Figure 2). The finding for the WOMAC scale values (Figure 3) and the Lequesne functional index values (Figure 4) were similar to those for VAS, showing a highly significant decrease over time (Friedman, $p < 0.001$) (Table II).

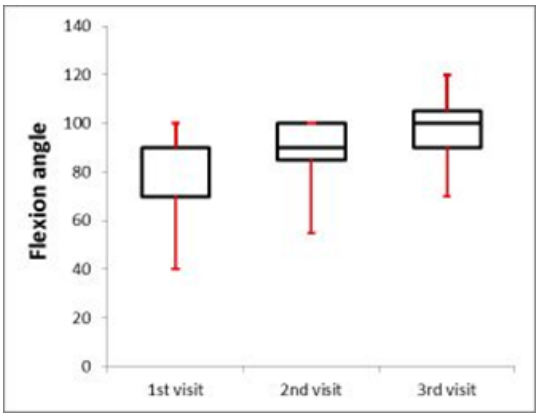

Figure 1.

Comparison of flexion angle values among the three visits

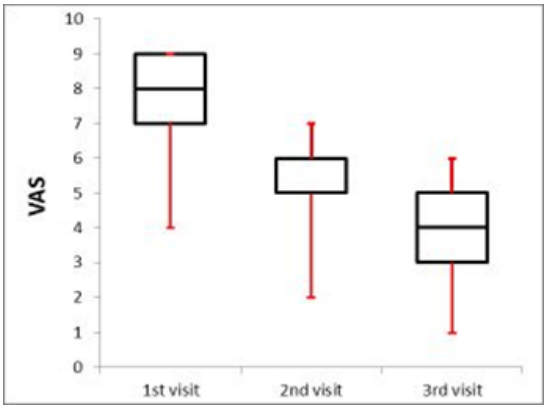

Figure 2.

Comparison of VAS values among the three visits

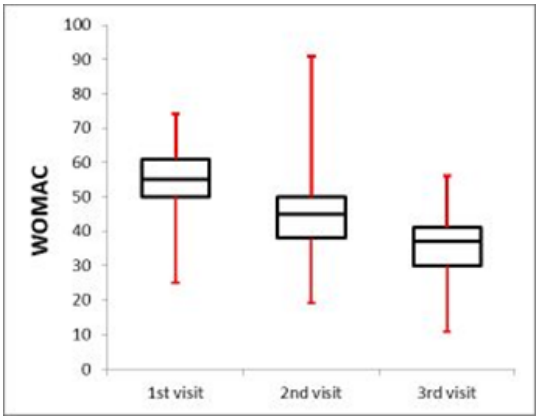

Figure 3.

Comparison of WOMAC values among the three visits

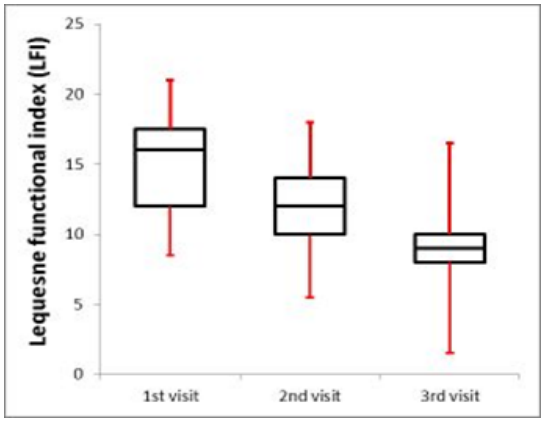

Figure 4.

Comparison of Lequesne functional index values among the three visits

Table II

Median and spread indicators for the study variables

Variable	Flexion angle			VAS		
Parameter	**T1**	**T2**	**T3**	**T1**	**T2**	**T3**
Minimum	40	55	70	4	2	1
1st Quartile	70	85	90	7	5	3
Median	90	90	100	8	6	4
3rd Quartile	90	100	105	9	6	5
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	5.5	1.5
1st Quartile	50	38	30	12	10	8
Median	55	45	37	16	12	9
3rd Quartile	61	50	41	17.5	14	10
Maximum	74	91	56	21	18	16.5

Analysing the correlation between the increase in the flexion angle and the decrease of the perceived pain or discomfort in performing day to day functions, using Spearman's rho correlation coefficient, we found the Lequesne functional index to show the greatest correlation to the flexion angle (ρ = -0.298) (Figure 5), followed by WOMAC scale (ρ = -0.278) (Figure 6) and VAS (ρ = -0.210) (Figure 7) (Table II).

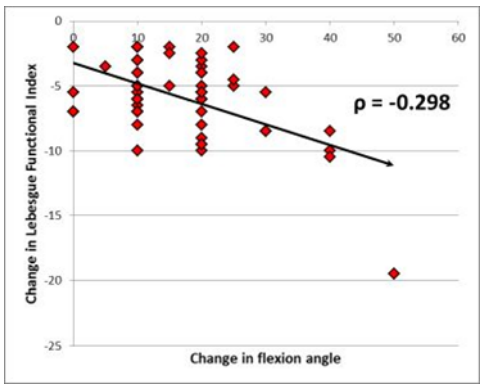

Figure 5.
Correlation between flexion angle changes and LFI changes during the study

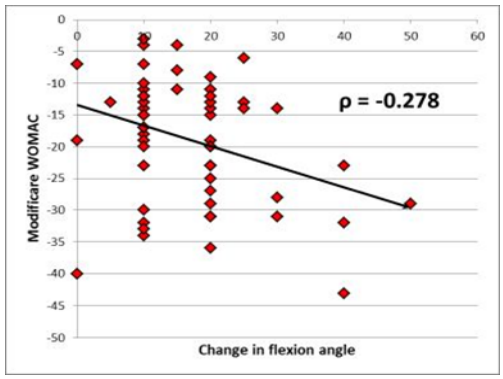

Figure 6.
Correlation between flexion angle changes and WOMAC changes during the study

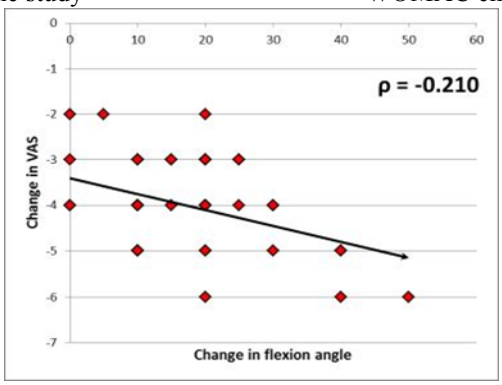

Figure 7.
Correlation between flexion angle changes and VAS changes during the study

Our study is the first clinical analysis in Romania to assess the efficacy of this complex herbal based on *Boswellia serrata* in KOA females. Our study confirms the significant repair of symptoms like aching, joint protrude, articular dysfunction and mobility in patients with OA due to these herbal extracts. None of the females reported any significant adverse effects during the six studied months. There was no adjustment in the lab parameters in the studied patients. Our observational study was performed taking into consideration an association between herbal treatment and rehabilitation program. The weakness of our study is the lack of a control placebo group, a difficult aspect in the rehabilitation medicine.

Going over the similar studies, it shows the various clinical benefits of derivates based on *Boswellia serrata* treatment in KOA patients, without age limits and supervised rehabilitation program [5]. The herbal tablets appear to be adequate and secure supplements for management of OA-patients [16], as it is proved in a double blind, placebo-controlled study conducted to test the efficacy of phytocomplex in terms of alleviating pain, inflammation and enhancing joint mobility and safety [7]. There were not reported negative effects by any of the patients [27]. The clinical efficacy and analgesic effect of the herbals was comparable to that of the commonly used drugs, diclofenac sodium and ibuprofen [26, 29].

For the last two decades, formulations of herbal complex tablet containing extracts of *Alpinia galanga*, *Commiphora wightii*, *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Tribulus terrestris*, and especially *Boswellia serrata*, proved to have anti-arthritic, anti-inflammatory, muscle relaxant, immunomodulatory and analgesic roles [11].

The product used in our study is polyherbal, containing extracts of *Boswellia serrata*, *Commiphora wightii*, *Alpinia galanga*, *Glycyrrhiza glabra*, *Tribulus terrestris* and *Tinospora cordifolia*.

Boswellia serrata is the primary and the most important component, which has been historically used in the treatment of OA. *Boswellia serrata* gum resin extract (BSE) containing boswellic acids (BAs) is the main bio-active principle. These BAs extracts have demonstrated their anti-inflammatory and anti-arthritic roles, with good management of musculo-skeletal pain and inflammation, due to various mechanisms of action like avoidance of decreased glycosaminoglycan synthesis, inhibition of inflammatory mediators and recovered blood supply to joint structures [1, 6]. *In vitro* studies revealed that the boswellic acids, a group of penta-cyclic triterpenoid compounds, and their acetylated derivatives inhibit the biosynthesis of leukotrienes, the proinflammatory 5-lipoxygenase products which cause increased permeability [8, 34]. In addition, 3-acetyl-11-ketobeta-boswellic acid (AKBA) is a natural inhibitor of the transcription factor NFkB, whose attendance is a requirement for the formation/action of chemokines/cytokines involved in inflammatory reactions. This natural product also simultaneously reduces oxidative stress [36]. According to a Cochrane systematic review, BSE presents some benefits in the management of osteoarthritis, coupled with low side consequences, in clinical, placebo-controlled studies [11].

Alpinia galanga (galangal) is a common plant in the Southeast Asia. Phenolic compounds such as phenolic acids and flavonoids are the major constituents of this plant. The extracts of *Alpinia galanga* showed a complex role in the biochemical human status: platelet-activating factor (PAF)-inhibitory, acetyl-cholinesterase-inhibitory, antibacterial, antimicrobial, antifungal, antioxidant and apoptosis activities [26, 27].

Commiphora wightii (*C. mukul*) is a well-known medicinal plant since 3000 years ago, having well-known biological properties [10, 27]. *C. wightii* contains a bitter gum known as Guggul (Myrrh) in stems and leaves. The pharmacological activities associated with Guggul gum include antibacterial, anti-inflammatory, antirheumatic, COX inhibitory, anticoagulant and hypolipidaemic actions that are mostly due to the existence of steroids compounds [20, 38].

Glycyrrhiza glabra (licorice) has been regarded as an herbal product since ancient periods. Nowadays, it is a well-recognized spice that has good pharmacological effects [22]. Licochalcone A (Lico A), a flavonoid compound detected in the licorice root, has been mentioned to activate Nrf2 signalling pathway and to have anti-inflammatory activity in IL-1β-stimulated chondrocytes [14]. Phytochemicals are well accepted as sources of pharmacologically efficacious therapy in the management of some oxidative stress related diseases. Methanol fraction of *Glycyrrhiza glabra* demonstrated optimal scavenging activity against nitric oxide free radicals and DPPH, proportionally to standard antioxidants [12].

Tinospora cordifolia (herb guduchi) has been used for long for its *Rasayana* properties to increase the vigour and immunity [4]. It is found to be safe on haematological and biochemical organ function tests and has muscle strengthening and lipid lowering action in healthy individuals [9]. *Tinospora cordifolia* can be taken daily as a prophylactic agent to prevent the long-term biochemical changes in the body and related adverse consequences on the heart and other body systems due to chronic activation of the sympathetic nervous system [4]. Guduchi treatment acts on the macrophages, enhances the tumouricidal activity against L929 fibroblast cells and increases the production of nitric oxide. Two types of kinases - tyrosine-specific protein kinase and protein kinase C - have an important role in the tumoricidal function mediated by guduchi [21].

Tribulus terrestris. Many different components with a variety of chemical structures and biological activities have been isolated from *Tribulus terrestris*, including amino acids, amide derivatives, glycosides, flavonoids, phytosterols, proteins, steroidal saponins, tannins, and terpenoids. From all different types of compounds, flavonoids (derivatives of isorhamnetin, kaempferol and quercetin) and steroidal saponins (protogracillin and protodioscin) are described to be the most important metabolites with various bioactivities and unique biological activities and complex pharmacological activities for cardiac protection and providing anti-inflammatory, antidiabetic, anti-oxidants, antitumour and anti-urolithic outcomes, also improving the sexual function [37, 39]. Previous studies have indicated that the ethanolic extract of

*T. terrestris (*EETT) is efficient in controlling inflammation by regulating IL-6, IL-10, COX-2, tumour necrosis factor-α, and nitric oxide (NO) [24].

When herbal or medicinal plants are administered, we have to take into consideration the WHO guidelines for the definition of medicinal plant products [11]. All these medicinal plants may contain pro-inflammatory mediators and interact with various cytokines, at least under experimental studies. The mechanism of action of the oral herbal products seems to be similar to that of the non-steroidal anti-inflammatory drugs. Although their mechanisms of action have not yet been established, completely interactions with cartilage destruction and mediators of inflammation give an argument for using them as supplements in patients with OA. The active principle of a medicinal plant product is the sum of all ingredients that produce the medicinal action, namely the phytocomplex. Despite their advantages, herbals elevate some concerns, such as their bioavailability, the lack of standardization, the drug - herbal interactions, the insufficient regulatory guidelines at national and international levels [3, 25].

Conclusions

The complex herbal product, based on *Boswellia serrata*, used in the present study, helps alleviate the pain and disability caused by KOA, promoting normal strength and flexibility of muscle and connective tissue, with enhancing the quality of life.

Physical therapy and kinetic programs in association with herbals represent the best therapy for females with KOA, which obviously contributes to the control of a progressive and irrevocable out-growth of arthritis disease.

In the following years, the controlled studies may be guided to consider the complex role of the herbal product for the complete management of KOA patients, including other localisations of the disease (hand, hip), in accordance with international recommendations for the medical management of osteoarthritis.

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