Rumalaya forte and Reosto in Osteoarthritis: A combined study

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ABSTRACT
The study was carried out to determine the efficacy, tolerability and safety of Rumalaya forte and Reosto combination therapy in osteoarthritis and to compare the results with Rumalaya forte alone, both being polyherbal formulations. One hundred patients of either sex, between the ages of 40 to 70 years, fulfilling the American College of Rheumatology criteria for knee osteoarthritis and with clinical and radiological evidence of stage II and III osteoarthritis of knee joints along with involvement of other joints were included in the study and were divided into two groups on the basis of a computer generated random number allocation program. Group I received one tablet of Rumalaya forte and two tablets of Reosto, and Group II received one tablet of Rumalaya forte and 2 tablets of placebo for a period of 6 months. Pain, function and stiffness were assessed using WOMAC osteoarthritis index. Time taken to cover 10 meter distance, BMD score, VAS score and patient global assessment were assessed. The intention to treat population consisted of hundred patients. Both groups showed significant improvement in clinical characteristics viz., WOMAC osteoarthritis index, joint stiffness score, joint function score, walking assessment, BMD score and VAS score (p<0.01). However, difference between response of overall impression between the two groups was statistically significant (p<0.01), Group I performing significantly better than Group II. Absence of any adverse reaction and stable hematological and biochemical parameters till the completion of treatment suggested that the combination of Rumalaya forte and Reosto is safe for prolonged therapy and is well tolerated.

INTRODUCTION
Osteoarthritis and osteoporosis have their origin in multiple factors
ranging from genetic susceptibility, endocrine and metabolic status, to mechanical and traumatic injury.\(^1\) Relationship between these two are under review for over a decade or more. Osteoarthritis is defined by the American College of Rheumatology as a heterogenous group of conditions that leads to joint symptoms and signs, which are associated with defective integrity of articular cartilage in addition to related changes in the underlying bone at the joint margins. It is a common, age related, heterogenous group of disorders characterized pathologically by focal areas of loss of articular cartilage in synovial joints, associated with varying degrees of osteophyte formation, subchondral bone change and synovitis. Joint damage is caused by a mixture of systemic factors that predispose to the disease and local mechanical factors that dictate its distribution and severity. Acute and chronic insult, including normal wear and tear, age, obesity and joint injury may initiate an imbalance between matrix synthesis and matrix degradation in healthy cartilage that promotes chondroid loss and prevents cartilage self-repair.\(^2,3\)

The osteoarthritis is considered a disease of the cartilage, but more recent evidence suggests that subchondral bone is also involved in the pathogenesis, of both disease initiation and progression. For example, increased local bone turnover, decreased bone mineral content and stiffness, and decreased trabecular numbers have been observed in osteoarthritic subchondral bone structure compared with normal bone.\(^4,5\)

The Duncan-Hartley guinea pig model is a widely used spontaneous model of osteoarthritis progression.\(^6\) Several recent osteoarthritis studies have evaluated the model for the effects of antiresorptive agents like bisphosphonates. In a study guinea pig osteoarthritis model, the pyridinyl bisphosphonate resirdonate was shown to show disease progression, as measured by the size and severity of cartilage lesions and the size of osteophyte, by up to 40%.\(^7\) Based upon this preclinical study, a combined clinical trial was performed in order to evaluate the efficacy of Rumalaya forte and Reosto together as compared to Rumalaya forte alone in the management of osteoarthritis of knee joints.

Rumalaya forte is a polyherbal formulation of The Himalaya Drug Company, Bangalore. It contains herbs such as powders of \textit{Boswellia serrata, Commiphora wightii, Alpinia galanga, Glycyrrhiza glabra and extracts of Tribulus terrestris and Tinospora cordifolia.} Its efficacy and safety in long-term use and management of osteoarthritis is well documented.\(^8-10\)

Reosto is also a polyherbal formulation of The Himalaya Drug Company, Bangalore. It contains herbs such as powders of \textit{Commiphora wightii, Vanda roxburghii, Terminalia arjuna, Withania somnifera, Sida cordifolia, and Kukkutandavatv bhasma.} Its efficacy and safety in osteoporosis is also established.\(^11,12\)

The present study was aimed to evaluate the clinical efficacy, tolerability and safety of combination of Rumalaya forte and Reosto tablets in treatment and management of osteoarthritis as compared to Rumalaya forte alone in terms of symptomatic relief of osteoarthritis, prevention of osteoporosis and disability associated with osteoarthritis.

**PATIENTS AND METHODS**

**Study design**

This study was a randomized, double blind clinical trial, conducted at Aravali Medical and Research Center, Aravali, Vengurla Taluka,

<table>
<thead>
<tr>
<th>No. of joints</th>
<th>Group I</th>
<th>Group II</th>
</tr>
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<tbody>
<tr>
<td>One</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Two</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Three</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Four</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Five</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Six or more</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

\(t=44.606; p<0.01\) and \(*t=51.00; p<0.01\) as compared with the respective pre-treatment value
Sindhudurg District, Maharashtra, India. The study was a prospective trial of 6 months duration. The study was conducted in accordance with the Helsinki Declaration, and was approved by the ethical committee of the Medical Center. Patients entered the study after fulfilling the inclusion and exclusion criteria and signing an informed consent form.

**Inclusion criteria**
One hundred ambulatory patients of either sex, between the ages of 40 to 70 years, who attended the outpatient clinic of Aravali Medical Research Center, from September 2005 to June 2006 with clinical and radiological evidence of osteoarthritis of knees, along with hip and other joints, were included in the present study (Table 1). Prior to the study, all patients had clinical symptoms of osteoarthritis of the knees and/or hips over a period of 2 years. These patients had radiological evidence of osteoarthritis with findings like osteophytes, marginal lipping, narrowing of joint space and sclerosis of articular margins.

**Exclusion criteria**
Patients with severe hypertension, serious cardiac failure of grade III or more, hepatic or renal failure, endocrine disorders like hyperthyroidisms, hypogonadism or Cushings syndrome, patients on corticosteroids, methotrexate or heparin, diabetes, bone malignancy with pathological fractures, women receiving estrogen and hormone replacement therapy, rheumatoid arthritis and gout were excluded from the study.

**Study procedure**
All patients were randomized into two groups of 50 patients each, with the help of a computer generated random number allocation program. The study Group I received 1 tablet of Rumalaya forte and 2 tablets of Reosto twice daily and Group II received 1 tablet of Rumalaya forte and 2 tablets of placebo twice daily for a period of 6 months.

A detailed medical history of all patients was recorded and symptomatic evaluation was done using the scoring system (WOMAC osteoarthritis index, joint stiffness score, joint function score, walking assessment, BMD score, VAS score). The two groups were similar with regards to the demographic data, baseline parameters and pain scores. The total symptom score was based on the joints involved, degree of pain, joint swelling, stiffness and activity level. The total sign score was based on joint effusion, tenderness, crepitus, range of movements, synovial hypertrophy, muscle wasting, and joint deformity.

Blood chemistry investigations included complete hemogram, liver function tests, renal function tests, serum calcium, phosphorus and alkaline phosphatase estimation. Radiological examination of the affected joints was carried out for osteophytes, subchondral sclerosis, trabecular hypertrophy, thickening, subchondral fractures, cratering, cartilage proliferation, calcified cartilage layers, fibrosis, hypertrophy of tendons and muscle wasting was recorded.

All patients were examined for BMD of the right heel by DEXA (Machine name: Achilles Express Ultrasonometer, Lunar Corporation System, ACE-3323, Pin Code No. LNR-40239).

**Follow-up and Assessment**
The patients were followed-up for 6 months and a symptomatic evaluation was recorded after completion of each month. A complete clinical, biochemical, radiological evaluation and BMD studies were carried out at the end of 6 months.

**Primary and Secondary Outcome Measures**
The predefined primary outcome measure for efficacy was a decrease in the total sign and symptom score at the end of 6 months and the clinical evaluation done by assessment of free mobility of the

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**Table 2. Statistical analysis of background characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (Mean ± SD)</th>
<th>Group II (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55.14 ± 9.58</td>
<td>59.96 ± 9.18</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 17 (34%)</td>
<td>21 (42%)</td>
</tr>
<tr>
<td></td>
<td>Female 33 (66%)</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>No. of joints involved</td>
<td>3.9 ± 1.73</td>
<td>3.26 ± 1.51</td>
</tr>
</tbody>
</table>

**Figure 2. Significant improvement of joint stiffness in the pre- and post-treatment values of Group I and Group II**

![Graph showing joint stiffness improvement](image-url)

*Figures 46.95; p<0.01 and **Figures 45.66; p<0.01 as compared with the respective pre-treatment value.
joint(s) without causing joint discomfort or pain, improvement in BMD score and bone specific biochemical parameters. Secondary outcome measures were short- and long-term safety assessed by incidence of adverse events, patient compliance to therapy and improvement in laboratory parameters.

**Adverse Events**
All adverse events, reported or observed by patients, were recorded with information about the severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication were predefined as "unrelated" (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), "possible" (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and "probable" (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take <80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

**Statistical analysis**
Statistical analysis was done according to intention-to-treat principles. The reduction in pain and swelling scores, WOMAC osteoarthritis index, joint stiffness score, joint function score, time taken to cover up ten meter distance, BMD score, VAS score, and overall impression score were evaluated to differentiate between the two treatment groups by the Unpaired ‘t’

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### Table 3. Statistical analysis of clinical characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (Mean ± SD)</th>
<th>Group II (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
</tr>
<tr>
<td>WO MAC osteoarthritis index</td>
<td>3.16 ± 0.51</td>
<td>0.08 ± 0.34</td>
</tr>
<tr>
<td>t=44.606; p&lt;0.01</td>
<td></td>
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<tr>
<td>Joint stiffness</td>
<td>3.14 ± 0.50</td>
<td>0.14 ± 0.45</td>
</tr>
<tr>
<td>t=46.95; p&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint function score</td>
<td>2.98 ± 0.47</td>
<td>0.18 ± 0.48</td>
</tr>
<tr>
<td>t=49.00; p&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking assessment</td>
<td>3.34 ± 0.92</td>
<td>1.16 ± 0.62</td>
</tr>
<tr>
<td>t=20.60; p&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD score</td>
<td>(-)1.98 ± 1.12</td>
<td>(-)1.45 ± 1.11</td>
</tr>
<tr>
<td>t=23.62; p&lt;0.01</td>
<td></td>
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</tr>
<tr>
<td>VAS score</td>
<td>8.24 ± 1.03</td>
<td>2.12 ± 0.78</td>
</tr>
<tr>
<td>t=64.00; p&lt;0.01</td>
<td></td>
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</tbody>
</table>

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*Figure 3. Significant improvement of joint function score in the pre- and post-treatment values of Group I and Group II

**Figure 3.** Significant improvement of joint function score in the pre- and post-treatment values of Group I and Group II.

*P<0.01 and **P<0.01 as compared with the respective pre-treatment value.
test. Comparison of the two groups for baseline comparability of different parameters by Unpaired ‘t’ test was done. Changes in various parameters from baseline values after 6 months were evaluated by Paired ‘t’ test. The minimum level of significance was fixed at a 95% confidence limit and a 2-sided ‘p’ value of <0.05 was considered significant.

RESULTS

Background Characteristics

The demographic background of patients revealed preponderance of females over males in both the groups. In Group I, there were 66% females, whereas in Group II, it was 58%. The mean age of patients in Group I was 55.14 years and 59.96 years of patients in Group II. The mean number of joints involved was 3.9 for patients belonging to Group I and 3.26 for Group II. These differences were also statistically not significant (p>0.05) (Table 2).

CLINICAL CHARACTERISTICS

The WOMAC osteoarthritis index pre-treatment mean score was 3.16 and post-treatment mean score was 0.08 for Group I. While the WOMAC osteoarthritis index pre-treatment mean score was 2.96 and post-treatment mean score was 0.92 for Group II.

The mean change in pre- and post-treatment difference score of WOMAC osteoarthritis index was statistically significant for Group I (p<0.01). This difference was also statistically significant for Group II (p<0.01) (Table 3 and Figure 1).

The joint stiffness pre-treatment score was 3.14 and post-treatment score was 0.14 for Group I, whereas the joint stiffness pre-treatment score was 3.0 and post-treatment score was 0.88 for Group II. There was a statistically significant change in mean joint stiffness score of pre- and post-treatment for Group I as well as for Group II (p<0.01) (Table 3 and Figure 2).

The mean pre-treatment score of joint function was 2.98 and post-treatment score was 0.18 for Group I. The mean pre-treatment score of joint function was 2.96 and post-treatment score was 0.84 for Group II. There was statistically significant mean change in joint function score (p<0.01) for Group I and also for Group II (Table 3 and Figure 3).

Similar findings were observed for walking assessment score, BMD score and VAS score. There was statistically significant mean change in pre- and post-treatment score for Group I and also for Group II (p<0.01) in respect of above parameters (Table 3 and Figures 4, 5 and 6).

The hematological and biochemical analysis of blood were within normal limits for all the patients. No significant change was noted in the hematological and biochemical parameters at the end of the study.

There was remarkable improvement in the symptomatology and disability due to osteoarthritis in both the groups as is evident from WOMAC osteoarthritis index, joint stiffness score, joint function
assessment and walking assessment. However, the subjective and objective improvement in Group I was significantly higher as compared to Group II. There was improvement in BMD score in Group I as compared to marginal improvement in Group II.

The patient’s global assessment of arthritis confirmed the symptomatological and functional improvement in both the groups as compared to pre-treatment status. However, Group I had remarkable improvement as against Group II as per patient’s global assessment of arthritis (Table 4 and Figure 7).

DISCUSSION
Increased evidence of the role of subchondral bone in both initiation and progression of osteoarthritis has resulted in an interest in drugs that affect bone metabolism and might slow or even halt the process of joint degeneration. Similar encouraging consistent results were observed in the joint stiffness score, joint functional assessment score and walking assessment score. Significant improvement of BMD score, observed in the group receiving Reosto tablets along with Rumalaya forte tablets, is possibly responsible for overall encouraging results noted by the use of combination as compared to Rumalaya forte group. Clinical parameters and findings noted were further confirmed by patient’s global pain assessment score.

Statistical analysis of the clinical characteristics and overall impression support the view that the group receiving Rumalaya forte and Reosto tablets had significantly better clinical and functional results than those receiving only Rumalaya forte tablets although both the groups had significant improvement in the clinical and functional condition.

A Chi-Square test suggested that there was significant association between response of overall impression and the two groups. The difference was statistically significant ($p<0.01$). Group I (Rumalaya forte + Reosto tablets) performed significantly better than Group II (Rumalaya forte + Placebo tablets) in respect of overall impression.

The excellent symptomatic and functional results observed with the group receiving combination of Rumalaya forte and Reosto tablets might be due to a synergistic action of the two drugs. Rumalaya forte is known to have potent anti-inflammatory, antioxidant and decreased bone marrow abnormalities. Positive results were observed with Rumalaya forte treatment and combination of Rumalaya forte and Reosto treatment, with regard to symptomatic improvement, as assessed by the WOMAC osteoarthritis index, whereas the group receiving Rumalaya forte tablets alone showed less improvement as compared to the group receiving combination of Rumalaya forte with Reosto tablets.
immunostimulant actions, which result in excellent symptomatic benefits and better clinical management of osteoarthritis. Experimental evaluation of Reosto in animal models showed inhibition of bone resorption, stimulated new bone formation, thereby proving that it has a potential to be used as an anti-osteoporotic agent. Clinical trials on human subjects have indicated that there was a significant improvement in BMD and selected bone-specific parameters in all patients who received Reosto in short period of time.

Thus, the patients receiving combination therapy of Rumalaya forte and Reosto are exposed to synergistic action of the ingredients. 

*Boswellia serrata* has boswellic acid, which is the principle ingredient that blocks the synthesis of pre-inflammatory chemomediators, like 5-lipoxygenase and also reduces glycosaminoglycan degradation, essential to prevent articular damage. In addition, it has a strong immunostimulant activity. Menon and Karr have reported potent sedative and analgesic effects of *Boswellia serrata*.

*Commiphora wightii* has a dose-dependent anti-inflammatory activity and helps to control inflammation and pain in osteoarthritis patients. *Alpinia galanga* inhibits lipid peroxidation. It inhibits the release of pro-inflammatory cytokines (IL-1β, TNF-α, COX-2 and NF-Kappa-β). *Alpinia galanga* induces biphasic activity in membrane stabilization, which is a contributory mechanism for its anti-inflammatory activity observed in the study.

*Glycyrrhiza glabra* possesses anti-inflammatory and anti-allergic activity. The anti-inflammatory action might be due to the presence of terpinoids, i.e. glycyrrhizin and glycyrrhetinic acids.

*Tinospora cordifolia* protects against lipid peroxidation by its high reactivity towards DPPH, superoxide, and hydroxyl radicals. *Tinospora cordifolia* also causes a dose-dependent enhancement in complement-mediated immunity. The anti-complementary and immunomodulatory activities of *Tinospora cordifolia* are due to inhibition of C-3 convertase of the classical complement pathway.

*Terminalia arjuna* has been documented for its therapeutic efficacy in metabolic bone disorders. The active ingredients of *Terminalia arjuna* are arjutenoside, terminoside A arjunaphthanoleside (triterpeneglycosides), oleanolic acid and arjunic acid. The anti-inflammatory effect of *Terminalia arjuna* can be attributed to its potent antioxidant action.

*Withania somnifera* is an analgesic, which helps relieve pain associated with osteodystrophic disorders. The active ingredients of *Withania somnifera* are withanolides lactones, coumarin, scopoletin, aesculetin, beta-amyrin and phytosterols (stimasterol and sitosterol). Anti-inflammatory effects of *Withania somnifera* has also been documented along with its therapeutic potentials in chronic degenerative conditions. Potent antioxidant activity of *Withania somnifera* has been documented and it causes a significant inhibition of NO synthetase, protein synthesis and NF-κappa-β activation. It has anti-inflammatory activity in immune mediated inflammation and significant increase in white blood cells and platelet counts were observed with *Withania somnifera* pre-treatment. Goutam et al., documented immunopotentiating properties of *Withania somnifera*.

*Vanda roxburghii* is being used as a topical analgesic in rheumatic joint pains. It has remarkable anti-inflammatory effects.

*Sida cordifolia* contains natural phytoestrogens, which act as selective estrogen receptor modulators (SERMs). In addition, it has potent anti-inflammatory and analgesic effects. *Kukkutandatavak bhasma* is a rich organic source of calcium, which increases the absorption and bioavailability of calcium.

**CONCLUSION**

Osteoarthritis is a major public health problem resulting in chronic disability and there are only a few effective remedies available for its management. There is a potent synergistic action of ingredients of Rumalaya forte and Reosto, which has resulted in positive trends observed with combination therapy with regards to symptomatic, physical and functional improvement in management of osteoarthritis, as assessed by the WOMAC index, joint stiffness score, joint functional assessment score, walking, and pain in osteoarthritis patients.
assessment score, BMD score, VAS score, and patient global assessment score.

Combination therapy of Rumalaya forte and Reosto appeared to be safe for long-term usage, as there were no clinically significant adverse reactions recorded, and the hematological and biochemical parameters remained unaltered throughout the trial period.

To conclude, this study shows that the combination of Rumalaya forte and Reosto tablets is far superior as compared to Rumalaya forte tablets alone in the management of osteoarthritis, with overall encouraging results.

ACKNOWLEDGEMENTS
We take this opportunity to thank the management of Aravali Medical and Research Center for allowing us to conduct the trial and to make use of facilities provided by the center. We also thank all the staff of the center for their whole-hearted support and help during the course of the trial. We would like to put on record our special appreciation to the help extended by Miss. Survarna M. Warang, Staff Nurse and Miss. Kirti R. Karandikar, Laboratory Technician, for their untiring work and assistance, but for them the work would not have been completed. Lastly, a word of thanks and appreciation to The Himalaya Drug Company, Bangalore, for having extended whole-hearted assistance and help throughout the trial and thereafter.

REFERENCES


