Evaluation and Comparative Clinical Efficacy and Safety of Rumalaya Forte in Patients Suffering from Osteoarthritis of the Knee

Abstract
Although NSAIDs are commonly prescribed for the management of OA, numerous short- and long-term adverse events limit their usage. The present study was planned to evaluate the short- and long-term clinical efficacy and safety of Rumalaya forte, a polyherbal formulation, in patients suffering from OA of the knee.

This study observed a highly significant reduction in the mean symptom- and sign-score, which corroborated with the radiological improvements in the Rumalaya forte group. Also, there were no clinically significant changes in any of the hematological and biochemical parameters. Therefore, it may be concluded that Rumalaya forte is effective and safe in the long-term management of OA.

Evaluation_Himalaya.pm6 7/5/05, 4:02 PM19

Abbreviations
COX : Cyclo-oxygenase
DPPH : Diphenyl picryl hydroxy
IL : Interleukin
NF-kappa-β : Nuclear factor kappaβ
NSAID : Nonsteroidal anti-inflammatory drug
OA : Osteoarthritis
RA : Rheumatoid arthritis
TNF-α : Tumor necrosis factor-alpha
Clinical Study

Clinical evaluation was done after the completion of each month. A complete biochemical and radiographical evaluation was done at the end of the sixth month. The predefined primary efficacy endpoint was a decrease in the disease progression at the end of 6 months, while the secondary safety endpoints were incidence of adverse events, and patient compliance. All the adverse events were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Statistical analysis was done according to intent-to-treat principles.

This study observed a highly significant reduction in the mean symptom- and sign-score, which corroborated with the radiological improvements in the Rumalaya forte group. Also, there were no clinically significant changes in any of the hematological and biochemical parameters. Similarly, there were no clinically significant adverse reactions, and the overall compliance to the treatment was excellent. These observed beneficial effects of Rumalaya forte might be due to the synergistic actions of its ingredients, which have anti-inflammatory, anti-oxidant, and immunostimulant actions. Therefore, it may be concluded that Rumalaya forte is effective and safe in the long-term management of OA.

Introduction

There are only a few effective and safe remedies available for the management of OA. Although, nonsteroidal anti-inflammatory drugs are commonly prescribed for the management of OA, numerous short- and long-term adverse events (ranging from esophagitis, gastritis, peptic ulceration, hematopoietic disturbances and renal failure) limit their usage. Similarly, prolonged use of paracetamol for the symptomatic management of OA has a risk of hepatotoxicity.

Rumalaya forte is a polyherbal formulation recommended for the management of OA, and each Rumalaya forte tablet contains the powders of Boswellia serrata, Commiphora wightii, Alpinia galanga, and Glycyrrhiza glabra, the extracts of Tribulus terrestris and Tinospora cordifolia, and is processed in Vitex negundo and Zingiber officinale.

Aim of the study

The present study was planned to evaluate the clinical efficacy and safety (long- and short-term) of Rumalaya forte, in patients suffering from OA of the knee.

Study design

This study was a prospective, randomized, double-blinded, placebo controlled, phase III clinical trial, and was conducted at the Department of Orthopedic Surgery and Traumatology, Gandhi Medical College and Associated Hospital, Bhopal, India as per the ethical guidelines of Declarations of Helsinki. The study protocol, case record forms, regulatory clearance documents, product-related information, and informed consent forms were submitted to the “Institutional Ethics Committee” and were approved by the same.

Materials and methods

Inclusion criteria

One hundred ambulatory patients of either sex, who attended the outpatient clinic of the Department of Orthopedics, Gandhi Medical College, Bhopal, India, with clinical and radiological evidence of OA of the knee (tibiofemoral joint) were included in the study. All the patients had clinical symptoms of OA over a period of 2 years prior to the study, and were suffering from moderate-to-severe knee pain (with or without morning stiffness of < 30 minutes duration). These patients had radiological evidence of OA with findings like osteophytes, marginal lipping, narrowing of joint space, sharpened articular margin or sclerosis (damaged, thickened, eburnated subchondral bone or bone cysts).

Exclusion criteria

Patients with established hypertension, renal, hepatic or cardiac failure, patients on long-term corticosteroid treatment, patients with biochemical and clinical evidence of RA or gout, and those patients who were unwilling to give informed consent were excluded from the study.

Study procedure

All the patients were randomized into 2 groups of 50 patients each (Rumalaya forte and placebo groups) with the help of a computer generated random
number allocation program. A detailed medical history of all the patients was recorded, and symptomatic evaluation was done using the scoring system (sign- and symptom-score). The 2 groups were similar with regard to the demographic parameters and sign- and symptom-scores. The sign- and symptom-score parameters included total score, which was based on the number of involved joints, degree of pain, joint swelling, level of joint activity (e.g., difficulty in climbing steps), joint malfunction, and secondary muscle wasting. A complete systemic and joint examination and blood chemistry investigations (complete hemogram, liver function tests, and renal function tests) were done. Radiological examination of the affected joints was carried out for osteophytes, subchondral sclerosis, trabecular hypertrophy, thickening, fracture, cratering, cartilage proliferation, calcified cartilage layer, fibrosis, crystal deposition and viscosity of synovial fluid. Both the groups consumed 2 tablets of either Rumalaya forte, or placebo, as per the randomization plan, twice daily, for a period of 6 months.

Follow up and assessment

The patients were followed up for 6 months, and clinical evaluation was done after the completion of each month. A complete biochemical and radiographical evaluation was done at the end of the sixth month.

Primary and secondary endpoints

The predefined primary efficacy endpoint was a decrease in the disease progression as evident by the reduction in the sign- and symptom-scores at the end of 6 months. The secondary safety endpoints were incidence of adverse events, and patient compliance to the therapy.

Adverse events

All adverse events either reported or observed by the patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as “Unrelated”, “Possible” and “Probable”. Patients were allowed to voluntarily withdraw from the study, and for patients withdrawing from the study, efforts were made to ascertain the reason for dropout.

Statistical analysis

Statistical analysis was done according to intent-to-treat principles. Comparison of the two groups for baseline comparability was done by “Unpaired t Test”. The change in symptom- and sign-scores was evaluated by “Two-way repeated measures ANOVA Test”, which was followed by “Bonferroni’s post-tests” for evaluating the changes in various parameters from baseline values to the values after each month. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.005 was considered significant.

Results

All the enrolled 100 patients completed the study duration and there were no dropouts. There was no statistical difference in age of enrolled patients, in both the groups (t = 0.6403, p = 0.524; NS).

There was a highly significant reduction in the mean number of involved joints (F = 42.28, p < 0.0001; HS) (Table 1 and Fig. 1), joint swelling (F = 12.54, p < 0.0001; HS) (Table 1 and Fig. 2), pain (F = 10.6, p < 0.0001; HS) (Table 1 and Fig. 3), joint malfunction (F = 13.13, p < 0.0001; HS) (Table 1 and Fig. 4), secondary muscle weakness (F = 14.36, p < 0.0001; HS) (Table 1 and Fig. 5), and difficulty in climbing steps (F = 14.22, p < 0.0001; HS) (Table 1 and Fig. 6) in the Rumalaya forte group, from 2nd month onwards till the end of the study, while in placebo group no such trend was observed.

These observations were also corroborated with the radiological improvements in the mean scores for subchondral sclerosis (F = 3.56, p < 0.0001; HS), cortical buttressing (F = 4.686, p = 0.032; S), trabecular hypertrophy (F = 4.12, p < 0.0001; HS), wasting of muscles (F = 34.69, p < 0.0001; HS), cartilage proliferation (F = 4.007, p < 0.0001; HS), patchy inflammation (mild/chronic inflammation) (F = 14.12, p < 0.0001; HS), and in the number of osteophytes (F = 32.8, p < 0.0001; HS) (Table 2 and Fig. 7).
### Table 1

Comparative changes in arthritic parameters between Rumalaya forte (RF) and Placebo (P) groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of involved joints</th>
<th>Joint swelling</th>
<th>Pain</th>
<th>Joint malfunction</th>
<th>Secondary muscle weakness</th>
<th>Difficulty in climbing steps</th>
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<tr>
<td>F = 42.28, p &lt; 0.0001; HS</td>
<td>F = 12.54, p &lt; 0.0001; HS</td>
<td>F = 10.6, p &lt; 0.0001; HS</td>
<td>F = 13.13, p &lt; 0.0001; HS</td>
<td>F = 14.36, p &lt; 0.0001; HS</td>
<td>F = 14.22, p &lt; 0.0001; HS</td>
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<tr>
<td><strong>Time point</strong></td>
<td>RF</td>
<td>P</td>
<td>RF</td>
<td>P</td>
<td>RF</td>
<td>P</td>
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<td>Baseline</td>
<td>1.78</td>
<td>1.82</td>
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<tr>
<td>1st month</td>
<td>1.52</td>
<td>1.72</td>
<td>3.49</td>
<td>3.45</td>
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<tr>
<td>2nd month</td>
<td>1.14</td>
<td>1.62</td>
<td>3.16</td>
<td>3.35</td>
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<tr>
<td>3rd month</td>
<td>0.94</td>
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<td>2.65</td>
<td>3.42</td>
<td>2.58</td>
<td>3.42</td>
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<td>4th month</td>
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<td>2.08</td>
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<td>5th month</td>
<td>0.54</td>
<td>1.53</td>
<td>1.62</td>
<td>3.21</td>
<td>1.42</td>
<td>3.40</td>
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<tr>
<td>6th month</td>
<td>0.46</td>
<td>1.60</td>
<td>1.95</td>
<td>3.15</td>
<td>1.22</td>
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**Bonferroni’s post-test summary**

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<th>Baseline vs 1st month</th>
<th>RF</th>
<th>P</th>
<th>RF</th>
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<th>RF</th>
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<tr>
<td>F = 2.673, p &lt; 0.05; S</td>
<td>f = 0.8828, p = 0.05; S</td>
<td>f = 2.533, p = 0.05; S</td>
<td>f = 1.9401, p = 0.05; S</td>
<td>f = 0.4672, p = 0.05; S</td>
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<tr>
<td>t = 1.04, p &gt; 0.05; NS</td>
<td>t = 3.848, p &lt; 0.01; S</td>
<td>t = 1.755, p &lt; 0.05; S</td>
<td>t = 0.7535, p &gt; 0.05; S</td>
<td>t = 0.2398, p &lt; 0.05; S</td>
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<td>t = 2.025, p &gt; 0.05; S</td>
<td>t = 1.9401, p = 0.05; S</td>
<td>t = 0.4672, p = 0.05; S</td>
<td>t = 0.2398, p &lt; 0.05; S</td>
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<td>t = 1.9401, p = 0.05; S</td>
<td>t = 0.4672, p = 0.05; S</td>
<td>t = 0.2398, p &lt; 0.05; S</td>
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<td>t = 0.566, p &gt; 0.05; NS</td>
<td>t = 2.025, p &gt; 0.05; S</td>
<td>t = 1.9401, p = 0.05; S</td>
<td>t = 0.4672, p = 0.05; S</td>
<td>t = 0.2398, p &lt; 0.05; S</td>
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<td>t = 0.4672, p = 0.05; S</td>
<td>t = 0.2398, p &lt; 0.05; S</td>
<td>t = 0.566, p &gt; 0.05; NS</td>
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<td>t = 0.1918, p &gt; 0.05; NS</td>
<td>t = 0.0518, p &gt; 0.05; NS</td>
<td>t = 0.566, p &gt; 0.05; NS</td>
<td>t = 0.0518, p &gt; 0.05; NS</td>
<td>t = 0.1918, p &gt; 0.05; NS</td>
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<td>t = 0.0518, p &gt; 0.05; NS</td>
<td>t = 1.9401, p = 0.05; S</td>
<td>t = 0.4672, p = 0.05; S</td>
<td>t = 0.2398, p &lt; 0.05; S</td>
<td>t = 0.566, p &gt; 0.05; NS</td>
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<td>t = 0.1918, p &gt; 0.05; NS</td>
<td>t = 0.0518, p &gt; 0.05; NS</td>
<td>t = 0.566, p &gt; 0.05; NS</td>
<td>t = 0.0518, p &gt; 0.05; NS</td>
<td>t = 0.1918, p &gt; 0.05; NS</td>
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<td>t = 0.0518, p &gt; 0.05; NS</td>
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<td>t = 0.1918, p &gt; 0.05; NS</td>
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<td>t = 0.0518, p &gt; 0.05; NS</td>
<td>t = 0.1918, p &gt; 0.05; NS</td>
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patients or observed by the investigators), and the overall compliance to the treatment was excellent in both the groups.

**Discussion**

Osteoarthritis is a leading cause of chronic disability in the aging population, and the risk of disability attributable to OA of the knee is greater than risk of any other medical condition among the aged. Herbal medications have been used in the past for the effective management of OA.

This study observed a highly significant reduction in the mean number of involved joints, joint swelling, joint malfunction, joint pain, secondary muscle weakness and difficulty in climbing steps, in the Rumalaya forte group, from 2nd month onwards till the end of the study, while in placebo group no such trend was observed. These observations were also corroborated with the radiological improvements in the mean scores for subchondral sclerosis, cortical buttressing, trabecular hypertrophy, wasting of muscles, cartilage proliferation, pachymild/chronic inflammation, and in the number of osteophytes, in the Rumalaya forte group, from 2nd month onwards till the end of the study, while in the placebo group no such trend was observed. Also, there were no clinically significant changes in any of the hematological and biochemical parameters. There were no clinically significant adverse reactions, and the overall compliance to the treatment was excellent, in both the groups. These excellent beneficial actions of Rumalaya forte might be due to

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparative changes in “Radiological parameters” between Rumalaya forte and Placebo groups</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
<td><strong>Rumalaya forte</strong></td>
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<td></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Subchondral sclerosis</strong> <em>(F = 3.56, p &lt; 0.0001; HS)</em></td>
<td>Mean 2.13</td>
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<tr>
<td>Summary**</td>
<td>t = 4.39, p &lt; 0.001; HS</td>
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<tr>
<td><strong>Cortical buttressing</strong> <em>(F = 4.686, p = 0.032; S)</em></td>
<td>Mean 1.00</td>
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<tr>
<td>Summary**</td>
<td>t = 3.53, p &lt; 0.01; S</td>
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<td><strong>Trabecular hypertrophy/thickening</strong> <em>(F = 4.12, p &lt; 0.0001; HS)</em></td>
<td>Mean 1.35</td>
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<td>Summary**</td>
<td>t = 3.85, p &lt; 0.001; HS</td>
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<td><strong>Wasting of muscles</strong> <em>(F = 34.69, p &lt; 0.0001; HS)</em></td>
<td>Mean 3.00</td>
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<tr>
<td>Summary**</td>
<td>t = 10.00, p &lt; 0.001; HS</td>
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<td><strong>Cartilage proliferation</strong> <em>(F = 4.007, p &lt; 0.0001; HS)</em></td>
<td>Mean 1.35</td>
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<tr>
<td>Summary**</td>
<td>t = 4.27, p &lt; 0.001; HS</td>
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<tr>
<td><strong>Osteophytes</strong> <em>(F = 32.8, p &lt; 0.0001; HS)</em></td>
<td>Mean 2.84</td>
</tr>
<tr>
<td>Summary**</td>
<td>t = 10.1, p &lt; 0.001; HS</td>
</tr>
<tr>
<td><strong>Patchy inflammation (mild/chronic inflammation)</strong> <em>(F = 14.12, p &lt; 0.0001; HS)</em></td>
<td>Mean 2.13</td>
</tr>
<tr>
<td>Summary**</td>
<td>t = 6.80, p &lt; 0.001; HS</td>
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</tbody>
</table>

*Two-way repeated measures ANOVA test statistics summary; **Bonferroni’s post-test summary
Clinical Study

**Figure 1.** Comparative changes in “Number of involved joints” between “Rumalaya forte” and “Placebo” groups.

**Figure 2.** Comparative changes in “Joint swelling” between “Rumalaya forte” and “Placebo” groups.
Figure 3. Comparative changes in “Pain” between “Rumalaya forte” and “Placebo” groups.

Figure 4. Comparative changes in “Joint malfunction” between “Rumalaya forte” and “Placebo” groups.
**Clinical Study**

Figure 5. Comparative changes in “Secondary muscle weakness” between “Rumalaya forte” and “Placebo” groups.

Figure 6. Comparative changes in “Difficulty in climbing steps” between “Rumalaya forte” and “Placebo” groups.
Figure 7. Comparative changes in “Radiological parameters” between “Rumalaya forte” and “Placebo” groups.
the synergistic actions of its ingredients, which are well documented.

The active ingredients of *Boswellia serrata* are boswellic acids, monoterpenes, sesquiterpenes, diterpenes, and triterpene acids. The main ingredients of *Commiphora wightii* are flavonoids. The active constituents of *Alpinia galanga* are flavonoids, phenylpropanoids, and p-hydroxybenzaldehydes. The principle ingredients of *Glycyrrhiza glabra* are glabridin, and beta-glycyrrhetinic acid. The active ingredients of *Tripterygium wilfordii* are saponins (protodioscin) and a sitosterol glucoside. The active ingredient of *Tinospora cordifolia* is an arabinogalactan polysaccharide. The active ingredients of *Zingiber officinale* are gingerols, diarylheptanoids, and sitosterol glucoside. The active ingredient of *Glycyrrhiza glabra* is glycyrrhetinic acid.

*Clinical Study*

Rumalaya forte contains remarkable immunostimulant ingredients such as *Boswellia serrata*. Also, *Alpinia galanga* stimulates the reticulendothelial system. *Glycyrrhiza glabra* stimulates macrophages de novo, and inhibits the classical complement pathway. *Tinospora cordifolia* reduces the chemotactic activity of macrophages, and protects against myelosuppression with an increase in white blood cells and antibody titers. *Tinospora cordifolia* also causes a dose-dependent enhancement in complement-mediated immunity; and the anti-complementary and immunomodulatory activities of *Tinospora cordifolia* are due to inhibition of the C3-convertase of the classical complement pathway. *Tinospora cordifolia* also reverses chemically induced immunosuppression. The activation of macrophages by *Tinospora cordifolia* leads to an increase in granulocyte-macrophage colony-stimulating factor, which leads to leucocytosis and improves neutrophil function. *Tinospora cordifolia* also normalizes the phagocytic capacities of neutrophils. *Zingiber officinale* raises the thymus index, spleen index, phagocytosis, and rate of alfa-naphthyl acetate esterase (α-ANAE+) and immunoglobulin M titer, which all indicate immunostimulation.

This study observed the beneficial effects of Rumalaya.
forte, which might be due to the synergistic actions of its ingredients, such as anti-inflammatory actions of *Boswellia serrata*, *Alpinia galanga*, *Tinospora cordifolia*, *Vitex negundo*, and *Zingiber officinale*, antioxidant actions (*Commiphora wightii*, *Alpinia galanga*, *Glycyrrhiza glabra*, *Tinospora cordifolia*, *Vitex negundo*, and *Zingiber officinale*), and immunostimulant actions (*Alpinia galanga*, *Glycyrrhiza glabra*, *Tinospora cordifolia*, and *Zingiber officinale*). The unaltered blood chemistry, liver and renal function parameters suggest the long-term safety of Rumalaya forte in the management of OA.

**Conclusion**

Although NSAIDs are the commonly prescribed for the management of OA, numerous short- and long-term adverse events limit their usage. The present study was planned to evaluate the clinical efficacy and safety of Rumalaya forte, a polyherbal formulation, in patients suffering from OA of the knee.

This study observed a highly significant reduction in the mean symptom and sign score, which corroborated with the radiological improvements, in the Rumalaya forte group. Also, there were no clinically significant changes in any of the hematological and biochemical parameters. Further, there were no clinically significant adverse reactions, and the overall compliance to the treatment was excellent. These observed beneficial effects of Rumalaya forte might be due to the synergistic actions of its ingredients, which include anti-inflammatory, antioxidant, and immunomodulatory actions. Therefore, it may be concluded that Rumalaya forte is effective and safe in the long-term management of OA of the knee.

**References**

Clinical Study


