Evaluation of the clinical efficacy and safety of Rumalaya forte and “Glucosamine and chondroitin combination”, in patients suffering from osteoarthritis of the knee

ABSTRACT
There are only a few effective remedies available for the management of Osteoarthitis (OA), and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed agents. However, the use of NSAIDs is causally associated with various short- and long-term adverse events. Recently, glucosamine and chondroitin have acquired substantial popularity in the management of OA, and the present study was planned to evaluate and compare the clinical efficacy and safety of "Rumalaya forte" with "Glucosamine and chondroitin combination", in patients suffering from OA of the knee.

This study was an open, prospective, comparative, phase III clinical trial, and 110 patients of either sex, with OA of the knee were randomized into two equal groups, which were similar with regard to the demographic data, baseline parameters and pain scores. The total score was based on the number of joints involved, degree of pain, joint swelling, activity level, joint malfunction and secondary muscle wasting. Blood chemistry investigations and radiological examination of the affected joints was done in all patients. The 1st group consumed 2 tablets of Rumalaya forte, twice daily, and other group received 2 tablets of "Glucosamine and chondroitin combination" thrice daily for a period of 6 months. The predefined primary efficacy endpoint was a decrease in the total sign and symptom score, and secondary safety endpoints were incidence of adverse events, and

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>DPPH</td>
<td>Diphenyl-picrylhydrazyl</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
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<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
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<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor-alpha</td>
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<tr>
<td>S</td>
<td>Significant</td>
</tr>
<tr>
<td>NS</td>
<td>Non-significant</td>
</tr>
<tr>
<td>HS</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

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INTRODUCTION
Osteoarthritis (OA) is a major public health problem, and there are only a few effective remedies available for its management. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed agents for OA; however, the use of NSAIDs is causally associated with numerous short- and long-term adverse events (ranging from esophagitis, gastritis, peptic ulceration, hematopoietic disturbances, to renal failure). Similarly, prolonged use of acetaminophen for the symptomatic management of OA can lead to hepatotoxicity or nephrotoxicity. Recently “Glucosamine” and “Chondroitin” have acquired substantial popularity in the management of OA, but only a few comparative clinical trials have been conducted to generate the required evidence establishing their efficacy.

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, Glycyrrhiza glabra and the extracts Tribulus terrestris and Tinospora cordifolia and is processed in Vitex negundo and Zingiber officinale. The present study was planned to evaluate and compare the clinical efficacy and safety of Rumalaya forte with "Glucosamine and chondroitin combination", in patients suffering from OA of the knee.

METHODOLOGY
Aim of the study
The present study was planned to evaluate and compare the clinical efficacy and safety of Rumalaya forte with "Glucosamine and chondroitin combination", in patients suffering from OA of the knee.

Study design
This study was an open, prospective, comparative, phase III clinical trial, and was conducted at the Department of Orthopedic Surgery, K.G. Medical University, Lucknow, India as per the ethical guidelines of Declaration of Helsinki. The study protocol, case record forms, regulatory clearance documents, product related information, and informed consent were submitted to the "Institutional Ethics Committee" and were approved by the same.

MATERIALS AND METHODS
Inclusion criteria
One hundred and ten patients of either sex, who attended the outpatient clinic of the Department of Orthopedics, K.G. Medical University, Lucknow, 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, on long-term steroid treatment, with biochemical and clinical evidence of RA or gout and those who were unwilling to give informed consent were excluded from the study.

Study procedure
All the patients were randomized into 2 groups of 55 patients each (Rumalaya forte group, and "Glucosamine and chondroitin combination group") 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 data, baseline parameters and pain scores. The total score was based on the number of joints involved, degree of pain, joint swelling, activity level (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, crating, cartilage proliferation, calcified cartilage layer, fibrosis, crystal deposition and viscosity of synovial fluid. The 1st
Follow-up and assessment
The patients were followed up for 6 months, and clinical evaluation was done after completion of each month. A complete biochemical and radiographical evaluation was done at the end of the 6th month.

Primary and secondary endpoints
The predefined primary efficacy endpoint was a decrease in the total sign and symptom score at the end of 6 months, and the secondary safety endpoints were incidence of adverse events, and patient compliance to the therapy.

Adverse events
All adverse events reported or observed by 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", and the reduction in symptom- and sign-scores was evaluated by "Repeated Measure Two Way ANOVA Test", which was followed by "Bonferroni's post-tests" for evaluating the changes in various parameters from baseline values to the values after the 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.

Table 1: Age of patients in "Rumalaya forte" and "Glucosamine and chondroitin combination" groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rumalaya forte</th>
<th>Glucosamine and chondroitin combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>55.38</td>
<td>50.96</td>
</tr>
<tr>
<td>Std. Error</td>
<td>1.963</td>
<td>2.058</td>
</tr>
<tr>
<td>Unpaired 't' test summary</td>
<td>t=1.555, df=50, p=0.1262; NS</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS
Out of the 110 enrolled patients, 7 patients were lost to follow-up, and data of 53 patients from Rumalaya forte group and 50 patients from "Glucosamine and chondroitin combination" group was available for analysis. There was no statistical difference in age of enrolled patients, in both the groups (t=1.555, p=0.1262; NS) (Table 1).

There was a highly significant reduction in the mean number of involved joints in the Rumalaya forte group, from 2nd month onwards till the end of the study; while in "Glucosamine and chondroitin combination" group no such trend was observed (Table 2 and Figure 1).

There was a highly significant reduction in the mean score for joint pain (Table 2 and Figure 2), joint swelling (Table 2 and Figure 3), difficulty in climbing steps (Table 2 and Figure 4) in the Rumalaya forte group, from 2nd month onwards till the end of the study, while in the "Glucosamine and chondroitin combination" group, no such trend was observed.

There was a highly significant reduction in the mean score for joint malfunction (Table 2 and Figure 5), and secondary muscle wasting (Table 2 and Figure 6), in the Rumalaya forte group, from 2nd month onwards till the end of the study; while in "Glucosamine and chondroitin combination" group no such trend was observed.

There were no clinically significant changes in any of the hematological and biochemical parameters. There were no clinically significant adverse reactions (either reported by patients, or observed by the investigators), and the overall compliance to the treatment was excellent, in both the groups.

DISCUSSION
Glucosamine and chondroitin are well absorbed from the gastrointestinal tract, and they increase the proteoglycan synthesis in articular cartilage. Though glucosamine and chondroitin have been tested in various clinical trials, which demonstrated the efficacy in OA, considerable progress has been made in elucidating the methods used in these trials, which affect the validity of their conclusions. These studies have shown that trials with methodological flaws (especially inadequate allocation concealment and absence of intent-to-treat approaches) are associated with exaggerated estimates of benefit.

Glucosamine has been shown to alter chondrocyte metabolism in vitro, which is the rationale given for its use in OA; however, it is not known whether oral glucosamine can access chondrocytes, in vivo. Moreover, it is not known whether an effect on articular cartilage would translate into an effect on symptoms, given that there are no nerves in articular cartilage.

This study observed a highly significant reduction in the mean number of involved joints, and in the mean score for joint pain, joint swelling, difficulty in climbing steps, joint malfunction, and secondary muscle wasting, in the Rumalaya forte group, from 2nd month.
onwards till the end of the study, while in the "Glucosamine and Chondroitin combination" 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 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 diarylheptanoids, phenylpropanoids and p-hydroxybenzaldehydes. The principle ingredients of *Glycyrrhiza glabra* are glabridin (pyranoisoflavan) and beta-glycyrrhetinic acid. The active ingredients of *Tribulus terrestris* 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 oleoresins.

Table 2: Comparative reduction in arthritic parameters between "Rumalaya forte (RF)" and "Glucosamine and chondroitin combination (GCC)" groups

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>No. of involved joints</th>
<th>Joint pain</th>
<th>Joint Swelling</th>
<th>Difficulty in climbing steps</th>
<th>Joint malfunction</th>
<th>Secondary muscle wasting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RFGCC</td>
<td>RFGCC</td>
<td>RFGCC</td>
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</tr>
<tr>
<td>Baseline</td>
<td>2.42 ± 0.10 ± 2.00 ± 0.15</td>
<td>2.81 ± 0.17 ± 2.81 ± 0.17</td>
<td>2.85 ± 0.14 ± 3.00 ± 0.14</td>
<td>3.58 ± 0.01 ± 3.69 ± 0.11</td>
<td>3.39 ± 0.21 ± 3.35 ± 0.19</td>
<td>3.15 ± 0.10 ± 3.12 ± 0.15</td>
</tr>
<tr>
<td>1st month</td>
<td>2.15 ± 0.09 ± 1.89 ± 0.12</td>
<td>2.42 ± 0.11 ± 2.77 ± 0.13</td>
<td>2.15 ± 0.09 ± 2.65 ± 0.15</td>
<td>3.42 ± 0.11 ± 3.54 ± 0.11</td>
<td>2.96 ± 0.20 ± 3.04 ± 0.13</td>
<td>2.81 ± 0.12 ± 2.92 ± 0.12</td>
</tr>
<tr>
<td>2nd month</td>
<td>1.73 ± 0.09 ± 1.89 ± 0.12</td>
<td>1.85 ± 0.11 ± 2.42 ± 0.11</td>
<td>1.69 ± 0.11 ± 2.42 ± 0.11</td>
<td>3.04 ± 0.13 ± 3.35 ± 0.10</td>
<td>2.12 ± 0.15 ± 2.58 ± 0.15</td>
<td>2.46 ± 0.10 ± 3.04 ± 0.12</td>
</tr>
<tr>
<td>3rd month</td>
<td>1.50 ± 0.10 ± 1.96 ± 0.10</td>
<td>1.35 ± 0.10 ± 2.46 ± 0.10</td>
<td>1.39 ± 0.18 ± 2.42 ± 0.11</td>
<td>2.42 ± 0.10 ± 3.12 ± 0.11</td>
<td>1.50 ± 0.11 ± 2.81 ± 0.11</td>
<td>1.85 ± 0.10 ± 2.89 ± 0.12</td>
</tr>
<tr>
<td>4th month</td>
<td>1.12 ± 0.14 ± 2.08 ± 0.12</td>
<td>1.23 ± 0.14 ± 2.27 ± 0.09</td>
<td>1.39 ± 0.18 ± 2.42 ± 0.10</td>
<td>1.96 ± 0.14 ± 2.85 ± 0.14</td>
<td>1.00 ± 0.14 ± 2.81 ± 0.14</td>
<td>1.50 ± 0.10 ± 2.73 ± 0.13</td>
</tr>
<tr>
<td>5th month</td>
<td>0.73 ± 0.12 ± 2.00 ± 0.10</td>
<td>1.15 ± 0.10 ± 2.32 ± 0.14</td>
<td>0.81 ± 0.16 ± 2.27 ± 0.10</td>
<td>1.00 ± 0.17 ± 2.54 ± 0.10</td>
<td>0.65 ± 0.10 ± 2.62 ± 0.10</td>
<td>0.96 ± 0.12 ± 2.58 ± 0.13</td>
</tr>
<tr>
<td>6th month</td>
<td>0.46 ± 0.10 ± 1.73 ± 0.10</td>
<td>0.62 ± 0.14 ± 1.92 ± 0.10</td>
<td>0.50 ± 0.16 ± 1.69 ± 0.09</td>
<td>0.85 ± 0.14 ± 2.31 ± 0.10</td>
<td>0.42 ± 0.10 ± 2.81 ± 0.10</td>
<td>0.62 ± 0.10 ± 2.42 ± 0.10</td>
</tr>
</tbody>
</table>

Summary* F=40.45, p<0.0001; HS p<0.0001; HS p<0.0001; HS p<0.0001; HS p<0.0001; HS p<0.0001; HS

*Two-Way Repeated Measure ANOVA Test Summary

Figure 1: Comparative reduction in "Number of involved joints" between "Rumalaya forte" and "Glucosamine and chondroitin combination" groups
inflammatory cytokines (IL-1β, TNF-α, COX-2, and NF-κappa-β).

*Tribulus terrestris* is a potent inhibition of COX-2 activity.† *Tinospora cordifolia* reduces IL-1β production, and inhibits TNF-α.‡ *Vitex negundo* is also a strong anti-inflammatory agent.§

*Zingiber officinale* is a potent inhibitor of prostaglandin biosynthesizing enzyme (PG-synthetase), and arachidonate 5-lipoxygenase (an enzyme of leukotriene biosynthesis).

The ingredients of Rumalaya Forte have potent anti-oxidant actions. *Commiphora wightii* causes inhibition of nitric oxide formation, and it scavenges the effect of DPPH radicals.†* Alpinia galanga* inhibits lipid peroxidation.§* Glycyrrhiza glabra* has potent antioxidant activity, and the antioxidant effect of glabridin is due to hydrophobic hydroxyl moiety.†* Tinospora cordifolia* protects against lipid peroxidation by its high reactivity towards DPPH, superoxide and hydroxyl radicals, and it decreases the plasma thiobarbituric acid reactive substances and ceruloplasmin, along with an increase in the levels of glutathione and ascorbic acid.¶ *Vitex negundo* also has antioxidant action.¶* Zingiber officinale* has antioxidant effect comparable to ascorbic acid, and it lowers lipid peroxidation, while maintaining the activities of other antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase).¶

*Boeswilla serrata* has a strong immunostimulant activity. *Alpinia galanga* stimulates the reticuloendothelial (RE) system.¶* Glycyrrhiza glabra* stimulates macrophages de-novo, and inhibit the classical complement pathway.¶* Tinospora cordifolia* reduces chemotactic activity of macrophages, and protects against...
The activation of macrophages by *Tinospora cordifolia* leads to an increase in granulocyte-macrophage colony-stimulating factor (GM-CSF), which leads to leucocytosis and improves neutrophil function. *Tinospora cordifolia* also normalizes the phagocytic capacities of neutrophils. *Zingiber officinale* has immunostimulation actions, and *Zingiber officinale* raises the thymus index, spleen index, phagocytosis, and rate of alfa-naphthyl acetate esterase (α−ANAE+) and immunoglobulin M(IgM) titer, which indicates immunostimulation. The unaltered blood chemistry, liver and renal function parameters suggest the long-term safety of Rumalaya forte in the management of OA.

To summarize in the study, Rumalaya forte was found to be have more potent anti-inflammatory, antioxidant and immunostimulant actions, which might have resulted in excellent symptomatic benefits, and better clinical management of OA, as compared to “Glucosamine and chondroitin combination”.

**CONCLUSION**

Osteoarthritis is a major public health problem, and there are only a few effective remedies are available it’s management. Nonsteroidal anti-inflammatory drugs are the most commonly prescribed agents for OA; however, the use of NSAIDs is causally associated with numerous short- and long-term adverse events. Recently “Glucosamine” and “chondroitin” have acquired substantial popularity in the management of OA, but only a few comparative clinical trials have been conducted to generate the required evidence establishing their efficacy. The present study was planned to evaluate and compare the clinical efficacy and safety of Rumalaya forte with “Glucosamine and chondroitin combination”, in patients suffering from OA of knee.

This study observed a highly significant reduction in the mean myelosuppression with an increase in WBCs and antibody titers. *Tinospora cordifolia* also causes a dose-dependent enhancement in compliment-mediated immunity. 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
number of involved joints, and in the mean score for joint pain, joint swelling, difficulty in climbing steps, joint malfunction, and secondary muscle wasting, in the Rumalaya forte group, from 2nd month onwards till the end of the study, while in the "Glucosamine and chondroitin combination" 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 the synergistic actions of its ingredients, which are have potent anti-inflammatory, antioxidand and immunostimulant actions. Therefore, it may be concluded that Rumalaya forte is clinically effective and safe than "Glucosamine and chondroitin combination" in the management of OA of the knee.

REFERENCES

![Figure 6: Comparative reduction in "Secondary muscle wasting" between "Rumalaya forte" and "Glucosamine and chondroitin combination" groups](image-url)
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