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A prospective, open-label, non-randomised clinical trial to evaluate the safety and efficacy of Rymanyl Tablets in the treatment of Osteoarthritis

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ABSTRACT

Objectives: To evaluate the clinical efficacy and safety of Rymanyl Tablets in patients with knee osteoarthritis. **Material and Methods:** A prospective, interventional clinical study was conducted on 70 patients, aged between 18-60 years, confirmed with knee osteoarthritis and who were willing to give informed consent. All patients received Rymanyl Tablets at a dose of two tablets twice in a day for 90 days. All patients were evaluated at baseline and 90 days for improvement in knee flexion, quadriceps and hamstring muscle strength, 6-minute walk test score, European Q5D quality of life; reduction in knee swelling, pain intensity, WOMAC-pain, stiffness and physical function score and VAS pain scale. The Physician global assessment and Patient's global assessment (at end of the study) on efficacy and tolerability were made on a scale of 1- 5, namely, Excellent = 5, Good = 4, Fair = 3, Poor = 2 and Very Poor = 1. **Results:** Rymanyl Tablets could significantly improve all outcomes including improvement in knee flexion, quadriceps and hamstring muscle strength, 6-minute walk test score and European Q5D quality of life; reduction in knee swelling, pain intensity, WOMAC-pain, stiffness and physical function score and VAS pain scale. **Conclusion:** Rymanyl Tablets typically improve knee flexion, quadriceps and hamstring muscle strength, walking capacity, overall physical function and quality of life as well as reduce knee swelling, intensity of pain and stiffness, assessed at baseline and 90 days. There were no clinically significant adverse events either reported or observed during the entire study period.

Key words: *Rymanyl Tablet, Osteoarthritis, Joint pain, Ayurveda.*

INTRODUCTION

Osteoarthritis is the most prevalent form of arthritis, affecting millions of people worldwide. It is a degenerative joint disease characterized by the breakdown of articular cartilage and subchondral bone, leading to pain, stiffness and decreased mobility. This chronic condition primarily impacts the knees, hips, hands and spine; and its incidence increases with age.[1] Several risk factors contribute to the development and progression of osteoarthritis:

1. **Age:** The risk of osteoarthritis increases with age due to cumulative joint wear and tear.
2. **Gender:** Women are more likely to develop osteoarthritis, particularly after menopause, suggesting a hormonal component.
3. **Genetics:** Family history and genetic predisposition play crucial roles in susceptibility to osteoarthritis.
4. **Obesity:** Excess body weight increases mechanical stress on weight-bearing joints and contributes to systemic inflammation.
5. **Joint Injury:** Previous joint injuries, such as fractures or ligament tears, can lead to secondary osteoarthritis.
6. **Repetitive Stress:** Occupations or activities involving repetitive joint stress can accelerate cartilage wear.

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Epidemiology

Osteoarthritis most frequently occurs after age 30 years and prevalence increases steeply with age. Globally, 595 million people had osteoarthritis in 2020, equal to 7.6% of the global population. Compared with 2020, cases of osteoarthritis are projected to increase 74.9% for knee, 48.6% for hand, 78.6% for hip, and 95.1% for other types of osteoarthritis by 2050.[2] About 73% of people living with osteoarthritis are older than 55 years and 60% are females. With a prevalence of 365 million, the knee is the most frequently affected joint, followed by the hip and the hand. 344 million people living with osteoarthritis experience moderate or severe symptoms. With ageing populations and increasing rates of obesity and injury, the prevalence of osteoarthritis is expected to continue to increase globally.[3]

Pathophysiology

The pathophysiology of osteoarthritis involves complex interactions between mechanical, biological, and biochemical factors. The degradation of cartilage is a hallmark of the disease, driven by an imbalance between the synthesis and degradation of extracellular matrix components. Chondrocytes, the cells responsible for maintaining cartilage, undergo phenotypic changes, leading to increased production of degradative enzymes such as matrix metalloproteinases (MMPs) and aggrecanases. Additionally, inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) play significant roles in the progression of osteoarthritis by promoting catabolic processes and inhibiting anabolic activities within the joint.

Clinical Manifestations

Patients with osteoarthritis typically present with:

- **Pain:** Often described as a deep, aching pain exacerbated by activity and relieved by rest.
- **Stiffness:** Particularly noticeable after periods of inactivity or upon waking.
- **Crepitus:** A crackling or grating sensation during joint movement.
- **Swelling:** Mild to moderate joint swelling due to synovitis or effusion.
- **Decreased Range of Motion:** Limited movement due to pain, swelling, or joint deformity.

Diagnosis

Diagnosis of osteoarthritis is primarily clinical, supported by imaging and laboratory findings. Radiographic features include joint space narrowing, osteophyte formation, subchondral sclerosis, and cysts. Magnetic resonance imaging (MRI) can provide detailed visualization of soft tissue structures and early cartilage changes. Laboratory tests may be used to rule out other causes of joint pain, such as rheumatoid arthritis or gout.

Conventional Treatment

The management of osteoarthritis is multifaceted, focusing on alleviating symptoms, improving joint function and slowing disease progression. Treatment modalities include:

- **Non-pharmacologic Therapies:** Physical therapy, weight management and assistive devices.
- **Pharmacologic Therapies:** Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors and intra-articular corticosteroid injections.
- **Surgical Interventions:** In advanced cases, joint replacement surgery may be considered.

In general, oral and topical NSAIDs, including COX-2 inhibitors, are strongly recommended first-line treatments for osteoarthritis due to their ability to improve pain and function but are associated with increased risks in patients with certain comorbidities (e.g., heightened cardiovascular risks). Intra-articular corticosteroid injections are generally recommended for osteoarthritis management and have relatively minor adverse effects. Other treatments, such as capsaicin, tramadol, and acetaminophen, are more controversial, and many updated guidelines offer differing recommendations.[4]

Patients with osteoarthritis do not have access to a remedy that cures the degenerative changes to stop the recurrence of pain. Current therapeutics possess

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certain drawbacks, including the frustration of the patients due to the intolerance, non-adherence, ineffectiveness of drugs and possible side-effects. Studies have suggested a link between NSAIDs administration and inhibition of bone healing. NSAIDs seem to affect the transition phase of mesenchymal stem cells towards functional chondrocytes by inhibiting the expression of key molecules like TGF-β3.[5]

There is a lack of an effective and long-term treatment plan in the fight against osteoarthritis. There is a great need for the continuous development of new, safe and effective treatment of osteoarthritis. Among the many active compounds that have been studied for the treatment of osteoarthritis, extracts from plants and specific phyto-chemicals from natural resources have been of great interest in recent decades. Several studies evaluating osteoarthritis therapy based on natural sources revealed potential activity, especially in reduction of pain, stiffness and cartilage loss as well as improvement in physical function. Natural substances, in comparison with medicament, do not cause such adverse effects, which is the positive side of their use.

In the present study, Rymanyl Tablets, manufactured by Charak Pharma Pvt. Ltd. was studied for its efficacy and safety in patients with knee osteoarthritis.

Materials and Methods

Study Design

Prospective, non-randomised, open-label clinical trial.

Study Objectives

The main objective of the study was to evaluate the clinical efficacy of Rymanyl Tablets in Osteoarthritis. Further, the study also observed the clinical safety of Rymanyl Tablets in Osteoarthritis.

Inclusion Criteria

Participants, aged 18 to 60 years and visiting the outpatient department, diagnosed with knee osteoarthritis; Patients willing to provide informed consent; comply with study requirements, attending study visits and adhering to treatment protocols; having adequate understanding of the study procedures and ability to communicate effectively with study staff; to be available for the duration of the study period were enrolled in the study.

Exclusion Criteria

Individuals with significant comorbidities that could confound the study results, such as severe liver disease, respiratory disease, renal, hepatic, hematopoietic disease, hypertension, severe cardiac insufficiency, congestive heart failure, untreated hyperlipidemia (cardiovascular risk), or active malignancy; individuals with non-degenerative joint diseases or other joint degenerative diseases; pregnant or breastfeeding individuals; individuals who are incapacitated or bound to wheel chair or bed and unable to carry out self-care activities; individuals on current or recent (in the last 3 months) oral or intra-articular corticosteroid therapy; ongoing with anticoagulants, steroids, methotrexate and colchicine; individuals with pre-existing or recent onset of demyelinating disorders or type I diabetes; individuals receiving any investigational drug or participated in any other clinical trial that ended in preceding month or currently ongoing; individuals who needed high dose of NSAIDs or analgesics; individuals with active substance abuse, as this could affect compliance and confound results; individuals who are unlikely to comply with study protocols or follow-up visits were excluded. Individuals with any other condition or circumstance that, in the judgment of the investigator, would make the participant unsuitable for participation in the study were excluded. Patients could be withdrawn from the study at their own request or if they experience intolerable adverse events, show insufficient therapeutic effect, or needed deviations from the protocol at the discretion of the investigator.

Study Design

A non-randomized phase 4, prospective open label clinical trial in 70 patients diagnosed with osteoarthritis was planned following required GCP guidelines. After careful selection in terms of the eligibility criteria, screened subjects willing to enroll after explaining the clinical study procedure were requested to sign the Patient Consent Form. At baseline visit (0 day), Patient

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information sheet was provided to each subject in their language of preference. Case record form (CRF) was filled by the attending physician with complete medical history and required personal details of the subject at the start of the study. A thorough physical examination and necessary laboratory investigations were carried at baseline (0 day) and after completion of treatment (90 days).

Safety and efficacy evaluation of patients' clinical response to treatment was monitored from baseline till end of 90 days. All data were carefully entered in the Case Record Form provided. Side-effects were closely monitored in all patients. All adverse events were recorded by the investigator, and rated for severity and relationship to the study medication.

Clinical assessments

The patients were evaluated at baseline and 90 days after onset of treatment. Efficacy was evaluated on the basis of improvement in knee flexion, quadriceps and hamstring muscle strength, 6-minute walk test score, European Q5D quality of life; reduction in knee swelling, pain intensity, WOMAC-pain, stiffness and physical function score and VAS pain scale. The Physician global assessment and Patient's global assessment (at end of the study) on efficacy and tolerability were made on a scale of 1- 5, namely, Excellent = 5, Good = 4, Fair = 3, Poor = 2 and Very Poor = 1.

Intervention

Rymanyl Tablets, manufactured by Charak Pharma Pvt. Ltd. were studied for its efficacy and safety in patients with osteoarthritis, in a dose of two tablets twice in a day for 90 days. Rymanyl Tablets contain *Sida cordifolia, Vitex negundo, Ricinus communis, Withania somnifera, Boerhavia diffusa, Cyperus rotundus, Zingiber officinale* and *Piper longum.*

OBSERVATION

All 70 patients enrolled in the trial completed the study. Table 1 shows Demographic data of Patients at baseline who participated in our study before intervention. Table 2 shows outcome measures at baseline and 90 days from onset of treatment. After 90 days of treatment with Rymanyl Tablets, there was improvement in knee flexion, quadriceps muscle strength, hamstring muscle strength, 6-minute walk test score and European Q5D quality of life. Also, there was reduction in knee swelling, pain intensity, WOMAC-pain, stiffness, physical function score; and VAS pain scale. Table 3 & 4 shows laboratory findings and vital parameters of patients before and after treatment, respectively. Treatment with the Rymanyl Tablets did not lead to any abnormalities in the laboratory investigations and vital parameters as compared to the baseline values, reflecting its safety in knee osteoarthritis. Patients tolerated Rymanyl Tablets without any adverse events that needed discontinuation. Table 5 shows Global assessment of response by Physicians and Patients respectively after 90 days of treatment with Rymanyl Tablets.

Table 1: Demographic Data of Patients at Baseline

Patient characteristic		N = 70
Age (years)		53.09 ± 4.17
Gender	Male	45
	Female	25
Height (cm)		165.2 ± 12.54
Weight (kg)		64 ± 12.40
Body mass index (kg/m^2)		23.37 ± 3.95
Duration of knee osteoarthritis (months)		7.40 ± 3.53

Table 2: Outcome measures

Parameters	Baseline	After 90 days	p
Knee flexion (degree)	104.8 ± 16.8	111.2 ± 16.8	0.001*
Quadriceps muscle strength (N/m)	61.6 ± 19.1	68.1 ± 18.5	0.001*
Hamstring muscle strength (N/m)	63.7 ± 15.9	67.7 ± 18	0.007*
6-minute walk test score	218.0 ± 26.51	297.3 ± 27.89	0.0001*
European Q5D quality of life	6.3 ± 0.88	10.9 ± 1.71	0.0001*

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Knee swelling (cm)	40.8 ± 3.9	38.2 ± 3.9	0.001*
Pain intensity (cm)	5.0 ± 2.1	3.2 ± 2.1	0.001*
WOMAC-pain (score)	7.9 ± 4.2	6 ± 3.9	0.001*
WOMAC-stiffness (score)	1.6 ± 1.2	1.4 ± 1.4	0.130
WOMAC-physical function (score)	20.2 ± 10.7	16.3 ± 9.9	0.001*
VAS pain scale score	6.4 ± 1.24	3.7 ± 1.35	0.0001*

Table 3: Laboratory Safety Parameters

Parameters		Baseline	After 90 days	p
Bio-chemical	Haemoglobin (gm%)	13.223 ± 1.655	13.808 ± 1.791	0.062
	Haematocrit (%)	40.523 ± 3.707	41.469 ± 4.788	0.361
	Erythrocyte Count (RBC) (Mil/cum)	19.355 ± 18.850	15.315 ± 13.786	0.294
	Platelet Count (Lakh/cum)	2.681 ± 0.487	4.926 ± 8.496	0.364
	Luekocyte Count (WBC) (cells/cmm)	14559.46 ± 22356.02	8159.846 ± 1473.503	0.318
Renal function	Serum Creatinine (mg/dl)	0.769 ± 0.144	0.815 ± 0.141	0.387
	Uric Acid (mg/dl)	4.677 ± 0.741	4.631 ± 0.771	0.661
Liver function	Aspartate aminotransferase (IU/L)	18.769 ± 8.146	20.231 ± 7.507	0.318
	Alanine aminotransferase (IU/L)	22.692 ± 6.920	23.846 ± 6.479	0.178
	Alkaline Phosphatase (IU/L)	76.00 ± 26.115	82.385 ± 14.210	0.419
	Total Bilirubin (mg/dl)	0.618 ± 0.472	0.488 ± 0.259	0.381
	Serum glutamic pyruvic transaminase (IU/L)	22.71 ± 5.26	23.6 ± 4.75	0.42
	Serum glutamic oxaloacetic transaminase (IU/L)	23.6 ± 4.17	23.79 ± 3.51	0.76

Table 4: Vital Parameters

Parameters	Baseline	After 90 days	p
Systolic Blood Pressure (mmHg)	134.4	136.9	0.2675
Diastolic Blood Pressure (mmHg)	86.1	82.8	0.041
Heart Rate (per minute)	74.1	75.5	0.1053
Respiratory Rate (Breaths/minute)	19.8	21.8	0.036
Oral Temperature (° Fahrenheit)	98.1	98.4	0.1021

Table 5: Global assessment by Physicians & Patients after 90 days of treatment

Global assessment rating	Physician's assessment		Patient's assessment	
	n	%	n	%
Excellent	10	14	11	16
Good	56	80	54	77
Fair	1	1	2	3
Poor	3	4	3	4
Very Poor	0	0	0	0

RESULTS

Rymanyl Tablets could significantly improve all outcomes including improvement in knee flexion, quadriceps and hamstring muscle strength, 6-minute walk test score and European Q5D quality of life;

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reduction in knee swelling, pain intensity, WOMAC-pain, stiffness and physical function score and VAS pain scale.

Knee flexion improved from 104.8 ± 16.8 at baseline to 111.2 ± 16.8 degrees after 90 days of treatment with Rymanyl Tablets. Quadriceps and hamstring muscle strength improved from 61.6 ± 19.1 & 63.7 ± 15.9 at baseline to 68.1 ± 18.5 and 67.7 ± 18 N/m, respectively after 90 days of treatment. 6-minute walk test and European Q5D quality of life score improved from 218.0 ± 26.51 & 6.3 ± 0.88 at baseline to 297.3 ± 27.89 and 10.9 ± 1.71, respectively after 90 days of treatment. Knee swelling reduced from 40.8 ± 3.9 at baseline to 38.2 ± 3.9 cm after 90 days of treatment. Pain intensity assessed by VAS pain scale reduced from 6.4 ± 1.24 at baseline to 3.7 ± 1.35 after 90 days of treatment. WOMAC-pain, stiffness and physical function score reduced from 7.9 ± 4.2, 1.6 ± 1.2 and 20.2 ± 10.7 at baseline to 6 ± 3.9, 1.4 ± 1.4 and 16.3 ± 9.9, respectively after 90 days of treatment.

There were no significant differences in the vital parameters such as systolic and diastolic blood pressure, heart rate, respiratory rate and oral temperature; laboratory findings of bio-chemical parameters, renal function and liver function at baseline and 90 days after treatment.

The global assessment of response by physicians showed that 80% of patients showed a good improvement while another 14% showed excellent improvement in their condition by the end of 90 days of treatment. Similarly, 77% and 16% of the patients' global assessment indicated good and excellent response at the end of treatment, respectively. These findings confirm the efficacy of Rymanyl Tablets in the study population during the study period.

Discussion

Chronic pain is a major concern among people with osteoarthritis and can hinder a patient's quality of life, physical function and mental well-being. While no approved disease modifying therapies exist, pain management for individuals with OA is an evolving field. The management of osteoarthritis mostly involves targeting matrix-degrading proteases or senescent chondrocytes, promoting cartilage repair or limiting bone remodelling and local lowgrade inflammation.[6]

Notably, while many commonly administered NSAIDs have low rates of toxicity in controlled clinical trials, the strength of associations with adverse events are typically larger in observational studies. Oral NSAIDs are associated with toxicity involving gastro-intestinal, cardio-vascular and renal systems. Despite their potential for toxicity, oral NSAIDs remain the most frequently used pharmaceutical treatment for OA-related pain.[7]

The ongoing development of new agents, especially from natural plant/phyto source will provide additional management options, which in turn motivates discussion on how best to incorporate them into current treatment algorithms. Diverse approaches are recommended to manage osteoarthritis such as lifestyle modifications, diet intervention and pharmacotherapy. Despite the worldwide use of NSAIDs, their long-term efficacy is still questionable. Consequences of these drugs are arguable, due to their numerous adverse effects. Traditional herbal medicine represents an alternative and complementary approach for managing osteoarthritis because of its low toxicity and beneficial effects, such as anti-inflammatory and antioxidant effects. Recently, there is a tremendous awareness in patients and physicians to manage osteoarthritis with natural extracts. Large number of studies performed on the efficacy and safety of natural products, showed significant improvement in osteoarthritis outcomes. Medicinal formulations have shown promising effects in reducing pain and consequently improving function, making them new therapeutic options.[8]

In an experimental study ethanolic extract from the root and leaf of *Sida cordifolia* promoted osteoblast activity and prevented ovariectomy-induced bone loss in mice. It promoted osteoblastogenesis without any change in osteoclast differentiation. They restored the biomechanical strength of femur; improved both trabecular and cortical bone microarchitecture in mice after oral administration for 8 weeks. They exerted osteo-protective effect in ovariectomized mice by enhancing osteoblast activity and inhibiting osteoclast

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activity. *Sida cordifolia* extract could be a potential agent to have preventive and therapeutic effects on post-menopausal osteoporosis.[9] Another study investigated in-vitro free radical scavenging potential and in-vivo anti-osteoarthritic activity of *Sida cordifolia* L. (SC) and *Piper longum* L. (PL). SC and PL clearly attenuated OA-augmented expression of MMP and restored OA-reduced expression of TIMP in the synovium. This finding provides the first evidence that S. cordifolia and P. longum effectively operates through inhibition of cartilage matrix degradation in osteoarthritis.[10] A study demonstrated cartilage protective effect of Sida cordifolia L. and Zingiber officinale Rosc. through controlling MMPs and improving antioxidant levels in arthritic synovium in a rat model of collagenase-induced osteoarthritis.[11]

The seeds of *Vitex negundo* have been used for inflammation-related disease treatment in traditional medicine. A study focused on the anti-osteoarthritis (OA) effects of the total lignans of V. negundo seeds (TOV) in monosodium iodoacetate-induced osteoarthritis rats. TOV significantly attenuated osteoarthritis, leading to an increase in pain thresholds, improvement of knee articular cartilages and chondrocytes loss; decreased total joint scores, serum levels of TNF-α, interleukin-1β (IL-1β), and prostaglandin E2 (PGE2) in osteoarthritis rats. The main component vitedoin A alleviates osteoclast differentiation by suppressing ERK/NFATc1 signaling.[12] Increasing evidence has shown that NLRP3 inflammasome activation participates in chronic aseptic inflammation and is related to tissue fibrosis. The vital role of NLRP3 inflammasome, highly associated with tissue hypoxia, in the onset and development of knee osteoarthritis (KOA). Agnuside (AGN), a nontoxic, natural small molecule isolated from the extract of Vitex negundo L. (Verbenaceae), has been demonstrated to have antioxidant, anti-inflammatory, analgesic and many other properties. AGN alleviates synovitis and fibrosis in experimental KOA through the inhibition of HIF-1α accumulation and NLRP3 inflammasome activation.[13]

R. communis is widely distributed globally and is rich in bioactive phytoconstituents with multifaceted therapeutic roles. It modulates numerous inflammatory and biochemical markers and highlights its potential in the management of nociception and inflammation.[14]

Root extracts of *Withania somnifera* are known to possess analgesic, anti-inflammatory and chondro-protective effects. A study evaluated efficacy and tolerability of a standardized aqueous extract of roots plus leaves of *W. somnifera* in patients with knee joint pain and discomfort. At the end of 12 weeks, compared to baseline and placebo, significant reductions were observed in mean Modified WOMAC and Knee Swelling Index (KSI) with *W. somnifera* (250 and 125 mg) groups. Visual Analogue Scale (VAS) scores for pain, stiffness and disability were significantly reduced in *W. somnifera* (250 and 125 mg) groups. *W. somnifera* 250 mg group showed earliest efficacy at 4 weeks.[15]

CONCLUSION

The present interventional study indicates that Rymanyl Tablets are effective and safe in controlling signs and symptoms of knee osteoarthritis. There were no clinically significant adverse events either reported or observed during the entire study period. The overall compliance with the treatment was good and no treatment discontinuations were reported. Rymanyl Tablets typically improve knee flexion, quadriceps and hamstring muscle strength, walking capacity, overall physical function and quality of life as well as reduce knee swelling, intensity of pain and stiffness. Rymanyl Tablets aim at reducing the symptoms of osteoarthritis with an alternative approach to reduce further cartilage damage.

Cost of Study

All medications required during the 90 days of trial were provided by the sponsor. Charak Pharma Pvt. Ltd. reserves all rights over any publications of the study during the course and post completion.

Conflict of Interest

To avoid any conflict of interest, study was carried out under the unbiased supervision of Laxmi Clinic HCP who are not associated with the sponsors.

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