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Original Research Article

Effectiveness and NSAID sparing effect of combination of Rosehip, IridoForce and Aflapin for knee osteoarthritis (BRATO 3.0)

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Abstract

Background: Osteoarthritis (OA) is a progressive condition that affects the joints, leading to their gradual degeneration causing stiffness, pain, and mobility issues. Conventional treatments, such as NSAIDs, have significant side effects, leading to interest in nutraceutical alternatives. TriNyros, a combination of Rosehip, IridoForce, and Aflapin, may provide relief with fewer adverse effects. This study aimed to observe the potential NSAID-sparing effect of this combination in patients with OA.

Materials and Methods: The study was a prospective, open-label, real-world evidence program involving 136 OA patients who received TriNyros twice daily for 90 days. Key outcomes included changes in WOMAC scores for stiffness, pain, VAS pain scores, physical function and NSAID usage.

Results: By day 15, 67% of participants reduced NSAID or paracetamol use, and 27.94% maintained symptom control on the combination alone for 90 days. WOMAC scores decreased by 87% ($P<0.05$), with significant reductions in VAS pain scores ($P<0.05$). TriNyros was well-tolerated, with no major adverse events reported.

Conclusion: The combination of Rosehip, IridoForce, and Aflapin effectively alleviated OA symptoms and reduced reliance on conventional pain medications.

Keywords: Osteoarthritis, TriNyros, Rosehip, IridoForce, Aflapin, WOMAC score, VAS pain score, Joint pain.

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1. Introduction

Osteoarthritis (OA) is a prevalent form of arthritis and a chronic, degenerative, and disabling condition involving complex pathological changes within the entire synovial joint. It is characterized by structural deterioration of hyaline articular cartilage, progressive loss of subchondral bone integrity, synovial tissue hypertrophy increased synovial vascularisation, and instability of tendons and ligaments. As of 2021, more than 22% of adults over the age of 40 were diagnosed with knee OA, and the condition currently affects an estimated 500 million individuals worldwide.[1] Knee OA is a major contributor to disability in older adults globally, affecting 28.7% of the population in India. OA commonly impacts the hands, feet, spine, and major weight-bearing joints, particularly the knees and hips. Key risk factors constitute advancing age, being female, obesity, lack of physical activity, knee misalignment, frequent activities like kneeling, climbing, squatting, heavy lifting, and participation in strenuous or high-intensity sports that may lead to knee injuries.[2,3] OA is clinically characterized by joint functional impairment, stiffness, pain, and limitations in activities such as walking or running. Physical examination of OA patients may reveal bony enlargement, joint swelling, and signs of inflammation. Radiographic assessments, including magnetic resonance imaging (MRI), can detect key structural abnormalities such as marginal osteophyte formation, joint space narrowing, osteochondral tissue degradation, and other OA-related lesions. Among these symptoms, pain is the most prominent and often the primary reason patients seek medical attention.[1] Moreover, OA is often accompanied by comorbidities such as stroke, peptic ulcers, and metabolic syndrome, which comprises hypertension, dyslipidemia, diabetes mellitus, osteoporosis and hypothyroidism.[4] Diagnosis involves evaluating the patient's history (pain, short morning stiffness, and functional impairments),

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physical examination (limited or painful movement, bony enlargement, crepitus and joint tenderness). The diagnostic criteria for knee OA established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) are widely used globally.[5]

Progression of OA is driven by synovial inflammation, which is regulated by the 5-lipoxygenase (5-LOX) pathway, proinflammatory cytokines, and matrix metalloproteinases (MMPs). The enzymes break down the cartilage matrix, accelerating joint degeneration and making the condition worse.[6-8] Dysregulation of signaling pathways, including tumour necrosis factor-like weak inducer of apoptosis (TWEAK)/fibroblast inducible factor 14 (Fn14), tumour necrosis factor-alpha (TNF-α)/TNF-α receptor (TNF-αR), and interleukin-6 (IL-6)/IL-6 receptor (IL-6R), contributes to chondrocyte senescence and degradation of joint tissues. Activation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and signal transducer and activator of transcription 3 (STAT3) further drives the inflammatory cascade, promoting cartilage breakdown and synovial hypertrophy.[9]

Chondrocytes, the primary cells responsible for cartilage maintenance, secrete enzymes such as A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) and matrix metalloproteinases (MMPs), which regulate cartilage homeostasis. Overexpression of ADAMTS-7, ADAMTS-12, and MMP-13 is associated with OA progression, leading to extracellular matrix degradation. Biomarkers such as chitinase-3-like-protein-1 (CHI3L1), cartilage acidic protein-1 (CRTAC1), and high-temperature requirement A serine peptidase-1 (HTRA1) have been identified in synovial fluid, providing potential diagnostic and prognostic indicators of OA. Additionally, skeletal muscle signaling appears to influence periarticular structures, with increased muscle strength potentially mitigating OA symptoms.[9,10] The failure of traditional treatments such as NSAIDs, visco-supplementation, intra-articular corticosteroids and various other non-pharmacological therapies often stems from inadequate effectiveness and the risk of side effects associated with these interventions.[11-14] Non-traditional therapies are favored because of the cardiovascular and gastrointestinal adverse effects associated with NSAIDs.[15]

Nutraceuticals refer to dietary substances that help regulate anabolic and catabolic signals within joint tissues. Various compounds, including glucosamine, methylsulfonylmethane, chondroitin sulfate, curcumin, Boswellia, ginger, and collagen peptides, have been evaluated for their effectiveness in treating knee OA. However, the findings indicate uncertain efficacy and challenges related to their bioavailability and tolerability.[16-20] A review by Raju Vaishya et al. highlighted Aflapin and Rosehip among the top 10 nutraceuticals for knee OA in India.[21]

Rosehips (RHP) are the fruit of the *Rosa canina L*. plant, resembling small berries and contain an active compound called galactolipid (2S)-1, 2-di-O-[(9Z, 12Z, 15Z)-octadeca-9, 12, 15-trienoyl]-3-O-β-D-galactopyranosyl glycerol (GLGPG). Both RHP and GLGPG play a role in suppressing the catabolic processes that contribute to OA.[22]

IridoForce™ is an extract derived from the South African plant *Harpagophytum procumbens*, commonly referred to as Devil's Claw. The main active ingredient in IridoForce™ is harpagoside, a type of iridoid glycoside. It also contains other important substances, including procumbide, triterpenoids, sugars, aromatic acids, phytosterols, and flavonoids such as luteolin and kaempferol. Harpagoside demonstrates anti-inflammatory effects by inhibiting inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) through suppression of tumor necrosis factor-alpha (TNF-α) via the nuclear factor kappa B (NF-κB) pathway. IridoForce™ exhibits dose-dependent analgesic and antioxidant properties. Additionally, it protects cartilage by inhibiting COX-2, iNOS, and other pro-inflammatory mediators. Its action also involves suppression of matrix metalloproteinases (MMPs) and elastase, enzymes responsible for cartilage degradation.[23]

Aflapin® is an innovative formulation derived from the gum resin of *Boswellia serrata*, also known as Indian frankincense or Gajabhakshya. The main component responsible for its anti-inflammatory effects is boswellic acid (BAs).[24] Aflapin® works to reduce inflammation primarily by 5-LOX inhibition and suppression of leukotriene synthesis.[25] 3-O-acetyl-11-keto-β-boswellic acid (AKBA) is the most potent 5-LOX inhibitor among other BAs.[26,27] Likewise, Aflapin® function as a selective 5-LOX inhibitor and exhibits enhanced bioavailability compared to standard Boswellia extracts.[1,26]

Although this marks the third observational study of TriNyros, the objective of BRATO 3.0 was to observe the potential NSAID-sparing effect of TriNyros in patients with OA.

2. Materials and Methods

2.1. Study design

BRATO 3.0 was an open-label, prospective, observational, real-world evidence development initiative. The evaluation protocol received approval from the Suraksha Independent Ethics Committee, Mumbai, and the study was conducted in compliance with the Helsinki Declaration of 1975, as amended in 2000. Written informed consent was obtained from all participants prior to screening.

2.2. Inclusion and exclusion criteria

Participants were selected from an outpatient orthopedic clinic. The inclusion criteria required patients to be over 18 years old and to have a clinical diagnosis of knee OA

according to the guidelines established by the ACR. Additionally, they needed to report moderate to severe knee pain (a score of 5 or higher on a visual analog scale) during their most painful knee movement over the past month. Patients who did not achieve adequate pain control with NSAIDs were invited to join the study.

Exclusion criteria included patients with acute knee joint trauma, uncontrolled diabetes or hypertension, severe cardiac, renal, or hepatic diseases, or end-organ damage. Pregnant or lactating individuals, as well as those with a history of allergies to herbal products or NSAIDs, were also excluded from the study.

2.3. Study product

Participants were directed to two TriNyros capsules daily, with each capsule containing 275 mg of Rosehip, 100 mg of IridoForce™ (Devil's Claw extract), and 50 mg of Aflapin®, over a 3-month period.

Patients were on NSAIDs and paracetamol and continued with the combination TriNyros as an adjuvant to their treatment regimen. They were instructed to refrain from using other Ayurvedic, herbal, homeopathic, or alternative therapies during the treatment period and a record of all medications was kept.

2.4. Outcomes

Standardized case report forms were used for collecting data at screening, baseline, day 15, 30, 45, 60, and 90. The primary outcome measure included WOMAC Score for pain, mobility and joint function and pain; percentage of patients with decreased use of pain medication; percentage of patients not needing NSAID and maintained on TriNyros only. A visual analog scale (VAS) measuring 10 mm was used to evaluate pain at rest as well as during movement. The assessment of WOMAC, pain levels, and symptoms of OA was conducted on days 0, 15, 30, 45, 60, and 90.

2.5. Sample size and statistical analysis

Considering the study design of real-world evidence, a sample size of 120 patients was considered. Effectiveness and tolerability parameters were analyzed using the 'Intention to Treat' analysis. Demographic data were analysed using descriptive statistics. Differences in clinical response before and after the treatment was assessed for normal distribution using the Kolmogorov-Smirnov test. The paired Student's t-test was also used. For distribution-free data, the Mann-Whitney U test was used. All tests were carried out at 5% significance. The statistical methods of this study were reviewed by Markov Analytics, Pune.

3. Results

A total of 136 participants were enrolled with a mean age of 51.17± 3.36 years, out of which 77% were females. All the patients completed the study. The most common comorbidity was presence of both type 2 diabetes mellitus and hypertension (58%). Out of 136 patients, 46.32% were on oral paracetamol twice daily for pain relief (**Table 1**).

Table 1: Summary of demographic details

Parameter	**Baseline characteristics (n=136)**
Age - mean ± SD	
Gender – n (%)	
Males	31 (22.80%)
Females	105 (77.20%)
Comorbidity n (%)	
Type 2 diabetes mellitus and hypertension	79 (58.00%)
Type 2 diabetes mellitus and hypothyroidism	41 (30.14%)
Hypertension only	5 (3.67%)
Hypothyroidism and hypertension	9 (6.61%)
Others	2 (1.47%)
Pain medication n (%)	
Oral NSAIDs OD/BD once/twice weekly	27 (19.85%)
Topical NSAIDs QID	8 (5.88%)
Paracetamol (oral) BD thrice weekly	63 (46.32%)
No	38 (27.94%)

SD: Standard Deviation; n: Number of patients
OD, once daily; BD, twice daily; QID: four times daily; NSAIDs: non-steroidal anti-inflammatory drugs.

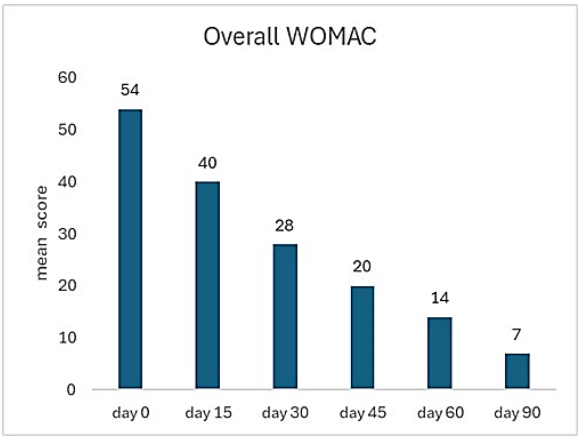

Figure 1: Change in total WOMAC score

3.1. WOMAC

The total WOMAC score reduced significantly by 87% from baseline to end of treatment ($P<0.05$). Improvement was observed from day 15 and persisted until day 90, with statistical significance ($P<0.05$) (**Figure 1**). The decrease in WOMAC score for pain, stiffness and physical function can be seen in **Figure 2**.

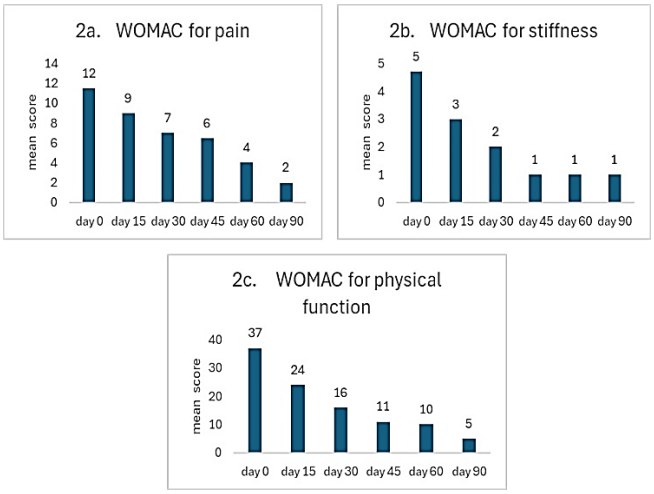

Figure 2: Changes in WOMAC scores for pain, stiffness and physical function; **a)**: Change in WOMAC score for pain; **b**): Change in WOMAC score for stiffness; **c)**: Change in WOMAC score for physical function

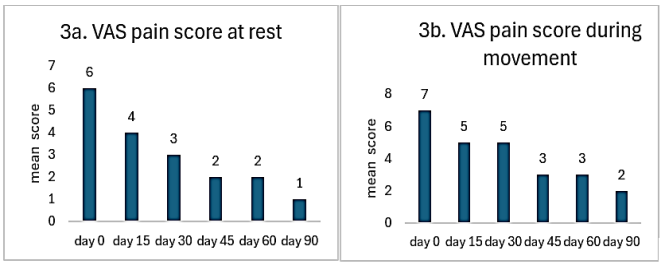

Figure 3: Change in VAS score; **a):** Change in VAS pain score at rest, **b):** Change in VAS pain score during movement

3.2. NSAID sparing effect

On day 15, a reduction in both NSAID and paracetamol dose/frequency was observed in 66 out of 98 patients. Thus, there was 67% NSAID-sparing effect. The dose reduction was seen from day 15 onwards and continued till 90 days. The 38 patients not on previous pain medication continued on the combination without the need for rescue therapy. Thus 27.94% of patients did not need NSAIDs and were maintained on TriNyros only during all the visits until day 90.

3.3. VAS pain score

VAS pain score at rest and during movement significantly reduced at the end of three months (P< 0.05) (**Figure 3**).

No major adverse events were observed. TriNyros was safe and well tolerated in patients with OA.

4. Discussion

The results from this study highlight the significant NSAID-sparing effect of TriNyros in managing OA symptoms. By day 15, 67% of patients (66/98) who were previously on NSAIDs or paracetamol exhibited a reduction in dose or frequency, with this effect persisting throughout the 90-day treatment period. This early and sustained reduction suggests that the combination may offer effective symptom control, reducing reliance on conventional pain medications, which are often associated with long-term side effects. Furthermore, 38 patients who were not on any prior pain medication were able to manage their symptoms solely with TriNyros, with no need for rescue therapy. Notably, 27.94% of the overall study population successfully maintained symptom control with the combination alone, further emphasizing its potential as a standalone treatment option in OA management. These findings underscore the dual benefit of TriNyros, not only in providing symptom relief but also in potentially minimizing the need for NSAIDs and other analgesics, which may improve overall patient safety and adherence. All patients reported significant improvement in WOMAC for pain, stiffness and physical function after three months of treatment.

The first observational study BRATO 1.0 by Chakraverty G et al., evaluated the significant reductions in WOMAC scores (67%), mobility, redness and VAS pain scores (67%) were observed, after three months of treatment (P< 0.05). Improvements were noted as early as day 15 and continued through day 90. The study did not report any major adverse reactions.[29] The second observational study of TriNyros by Tapaswi S evaluated its effectiveness in patients regardless of the presence of comorbidities. A total of 151 patients received the combination twice daily for 90 days. Results showed a significant reduction in WOMAC scores (66.12% and 66.57% for patients with and without comorbidities, respectively). ED-5D scores improved by 72%, and VAS scores decreased by 78.27%. Clinical symptoms also noted significant improvement, including pain on palpation, restricted mobility, and joint crepitus. Major adverse reactions were not observed. The study concluded that the combination of Rosehip, IridoForce, and Aflapin effectively reduces joint pain and improves mobility in OA patients, regardless of comorbidities.[30]

Our study was limited to patients experiencing moderate to severe knee pain, defined as a score of 5 or higher on a VAS during their most painful knee movement over the past month. We did not include patients with Grade 1 or Grade 4 based on arthritis grading criteria. Future studies will aim to incorporate these patient groups for a more comprehensive assessment.

5. Conclusion

In conclusion, the BRATO 3.0 study demonstrated that TriNyros, a combination of Rosehip, IridoForce, and Aflapin, effectively managed the symptoms of OA. Patients experienced a notable reduction in their reliance on NSAIDs or paracetamol, with many achieving symptom control on TriNyros alone over an extended period. Additionally, there was significant improvements in pain, stiffness, and physical function scores. Overall, TriNyros provided effective symptom relief, reduced the need for conventional pain

medications, and was well-tolerated, positioning it as a safe and effective option for managing OA symptoms.

6. Source of Funding

BRATO 3.0 Evidence Generation Program was sponsored by Nutragenix Healthcare Pvt. Ltd.

7. Conflicts of Interest

The authors declare no conflicts of interest.

8. Ethical Committee Approval

The study was approved by Suraksha – Independent Ethics Committee, Mumbai.

9. Acknowledgement

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