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Clinical benefits and risk assessment of TriNyros in osteoarthritis of the knee: BRATO evidence generation program

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Abstract

Background: Osteoarthritis is a major cause of disability worldwide, especially in older adults. Alternative treatments are preferred due to the cardiovascular and gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs). Nutraceuticals help in balancing anabolic and catabolic processes in the joint tissue, improve redox balance, free-radical scavenging, thus provide cartilage protection. *Rosa canina* L. (Rosehip), *Boswellia serrata* and *Harpagophytum procumbens* (Devil's claw) extract are being recognized for their anti-inflammatory, antioxidant, analgesic and chondroprotective properties in Osteoarthritis.

Aim: A post-marketing clinical evidence generation program was conducted to assess the effectiveness and tolerability of capsule TriNyros in knee osteoarthritis.

Methods: An evidence generation program was conducted in 20 outpatient orthopedic clinics. All patients received TriNyros containing [Rosehip 275 mg, Irido Force™ (Devil's claw extract) 100 mg and Aflapin® 50 mg] twice daily for 90 days. Patients were on their regular anti-arthritis treatment and TriNyros was added as an adjuvant to their regular treatment. Clinical assessment of symptoms included palpation pain, limitation of mobility, joint crepitus, swelling and redness was assessed. Osteoarthritis symptoms were measured using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), 3- pointer and 10mm visual analogue scale (VAS). Hematological and serum biomarkers were analyzed to evaluate tolerability of TriNyros.

Results: A total of 105 patients, comprising 42 women and 63 men mostly belonging to the age group of 58-65 years (39.05%) enrolled in the program. Significant reduction in WOMAC scores was seen in majority of the patients at day 15, 30, 60 and 90 ($P < 0.0001$). WOMAC scores for joint pain declined by 58.82% (mean \pm SD: 66.43 ± 11.97 to 27.35 ± 7.92) at the end of 3 months ($p < 0.0001$). The reduction was significant from the 15th day itself ($p = 0.02$) and continued till day 90. Pain measured by VAS significantly reduced by 67% (7.11 ± 1.56 to 2.34 ± 0.72 , $P < 0.0001$) at day 30, 60 and 90. At the end of the treatment, palpation pain, limitation of mobility, joint crepitus, swelling and redness showed significant improvements ($P < 0.01$). Intake of concomitant medication was observed in 32 (30.48%) patients. No major adverse reactions were reported.

Conclusion: Overall, this preliminary study concluded that TriNyros was found to be effective and well tolerated in reducing pain and improving general condition in osteoarthritis of the knee.

Keywords: Nutraceutical, osteoarthritis, aflapin, rosehip, devil's claw, real-world evidence (RWE)

Introduction

Core tip: Osteoarthritis (OA) of the knee is a major cause of disability in older adults worldwide, with a prevalence of 28.7% in India. It affects the hands, feet, spine, and large weight-bearing joints, such as the hips and knees. Risk factors include age, female sex, obesity, sedentary people, knee mal-alignment, frequent kneeling, squatting, climbing, heavy lifting, high-impact sports resulting in knee injury [1, 2]. Pathological changes include softening, ulceration, and finally, disintegration of the articular cartilage [3]. The key comorbidities associated with OA are stroke, peptic ulcer and metabolic syndrome that includes hypertension, diabetes mellitus, dyslipidemia, hypothyroidism and osteoporosis [4]. Clinical diagnosis is based on symptoms (pain, brief morning stiffness, and functional limitations) along with a physical examination (restricted or painful movement, joint tenderness, crepitus and bony enlargement).

American College of Rheumatology (ACR) or the European League against Rheumatism for knee osteoarthritis (EULAR) are recommended for appropriate diagnosis [5].

The onset of OA is a consequence of synovial inflammation influenced 5-lipoxygenase (5-LOX) pathway, proinflammatory cytokines and matrix metalloproteinases (MMPs) enzymatically degenerate cartilaginous matrix substances thereby aggravating the condition [6-8]. Failure of NSAIDs, viscosupplementation and intra-articular corticosteroids and other non-pharmacological interventions is attributed to a lack of efficacy and more adverse effects [9-12]. Alternative treatments are preferred due to the cardiovascular and gastrointestinal side effects of NSAIDs [13].

Nutraceuticals are dietary compounds that balance anabolic and catabolic signals in the joint tissue [14]. Glucosamine, chondroitin sulfate, methylsulfonylmethane, Boswellia, Curcumin, Ginger and collagen peptide have been tested in the treatment of knee OA with results showing ambiguous efficacy, poor bioavailability or poor tolerability [15-19]. Raju Vaishya *et al.* in their review mentioned Aflapin and Rosehip in the top 10 nutraceuticals used for Knee Osteoarthritis in India [3].

Rosehips (RHP) are the berry fruits of *Rosa canina* L. Galactolipid (2S)-1, 2-di-O-[(9Z, 12Z, 15Z)-octadeca-9, 12, 15-trienoyl]-3-O-β-D-galactopyranosyl glycerol (GLGPG) is the active constituent. RHP and GLGPG function in down-regulating catabolic processes that causes OA [20].

IridoForce™ is obtained from the extract of *Harpagophytum procumbens* (Devils claw), as traditional South African plant. Iridoid glycosides, primarily harpagoside, is the active constituent of IridoForce™. Harpagoside and procumbide, sugars, triterpenoids, phytosterols, aromatic acids and flavonoids such as luteolin and kaempferol are the other major constituents. Anti-inflammatory action of Harpagoside is due to inhibition of inducible nitric oxide (iNOS), cyclooxygenase (COX-2) expression by suppressing Tumor Necrosis Factor alpha (TNF-α) via nuclear factor kappa β (NF-κβ) pathway. Peripheral analgesic action and antioxidant action is dose-dependent. Chondroprotective action is conferred by inhibiting COX-2 and iNOS among other inflammatory mediators. Matrix metalloproteinases (MMPs) and elastase responsible for cartilage degradation are inhibited [21].

Aflapin® is a novel composition extracted from Boswellia serrata gum resin. (Indian frankincense or Gajabhakshya). Boswellic acid (BAS) is the main constituent contributing to anti-inflammatory property [22]. 5-LOX inhibition and suppressing leukotrienes is the main mechanism for reducing inflammation [23]. 3-O-acetyl-11-keto-β-boswellic acid (AKBA) is the most potent 5-LOX inhibitor among other BAS [24, 25]. Similarly, Aflapin® is a selective 5-LOX inhibitor [26]. Aflapin® has shown better bio-availability than Boswellia [1]. There is no existing data for the use of TriNyros in the treatment of osteoarthritis of the knee. This was the preliminary study to be undertaken to assess effectiveness and tolerability of TriNyros (Aflapin®, IridoForce™ and Rosehip) as an add-on treatment for patients who are on standard treatment and had inadequately controlled symptoms.

Methods

BRATO was a post-marketing clinical evidence generation program. The evaluation protocol was approved by Suraksha-Independent Ethics Committee, Mumbai. Participants were recruited from September 2019 until March 2020 and

followed up for 3 months. All participants gave written informed consent before the screening.

Setting and participants

Patients were recruited from 20 separate outpatient orthopedic clinics. Eligible patients were aged 19-75 years of age; clinical diagnosis of osteoarthritis of the knee based on the American College of Rheumatology (ACR) criteria and at least moderate pain in the knee (rated at 5 or greater by the subject on a visual analog scale) during the most painful knee movement during the last month. Patients who were inadequately controlled with NSAIDs were enrolled.

Exclusion criteria were acute joint trauma of the knee; uncontrolled diabetes and hypertension; any severe cardiac, renal and hepatic disease, or end organ damage; pregnancy or lactation; a history of allergy against herbal products, or NSAIDs.

Intervention

Subjects were instructed to take TriNyros capsule [Rosehip 275 mg, IridoForce™ (Devil's claw extract) 100 mg and Aflapin® 50 mg] twice daily for 3 months.

Patients were on their regular anti-arthritis treatment and TriNyros was added as an adjuvant to their regular treatment. Patients were advised not to take other Ayurvedic/herbal/homeopathic dietary supplements or any alternative therapies during the treatment period. A record of these medications was maintained.

Outcomes and Follow-up

Data were collected using standardized case report forms at screening; baseline; day 15, 30, 60 and 90. The primary outcome measures included OA symptoms, WOMAC score and pain. Clinical assessment of symptoms which included pain on palpation, limitation of mobility, joint crepitus, swelling and redness were assessed using a 4-point-scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe). Symptoms of osteoarthritis were assessed by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index and a higher WOMAC score represents worse symptom severity. The patients used the 10 mm visual analog scale (VAS) to assess pain. WOMAC, pain and OA symptoms were assessed at day 0, 15, 30, 60 and 90.

Hematological and serum biomarkers (ESR, CRP, CBC, SGOT, SGPT, urea, creatinine) and occurrence of adverse events were secondary outcome measures assessed at the beginning and end of the treatment. Blood pressure, heart rate and respiratory rate were monitored and measured during each visit.

Statistical analysis

Sample size considerations

This was the first clinical evidence generation program to evaluate the effectiveness and tolerability of TriNyros in knee osteoarthritis with no previous data available. A sample size of 100 participants from 20 centers (5 from each site) was considered adequate to address the evaluation objectives.

Effectiveness and Tolerability analysis

The effectiveness and tolerability data had been analyzed using 'Intention to Treat' analysis. Demographic data were analyzed using descriptive statistics. The Difference 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.

Results

A total of 105 patients, comprising 42 women and 63 men

were enrolled in the program. Maximum patients (39.05%) belonged to the age group of 58-65 years (n=41/105) as shown in Figure 1.

All patients received TriNyros capsule. The mean history of analgesic use (before treatment) was observed to be 42.86% (n=45). Intake of concomitant medication was observed in 32 (30.48%) patients.

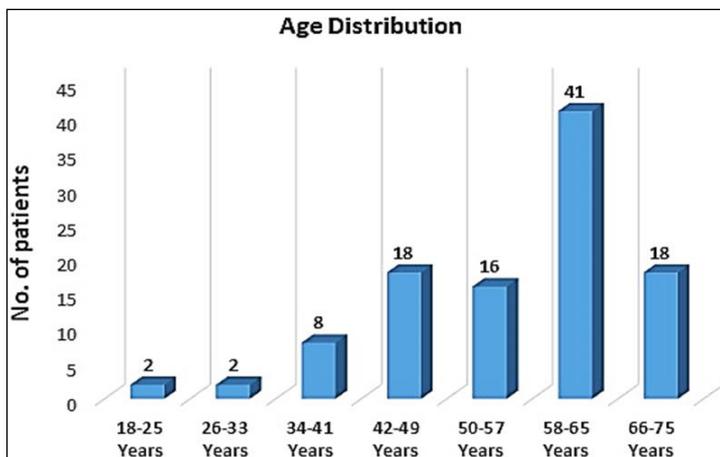


Fig 1: Age distribution of patients

WOMAC score

Before and after treatment scores for WOMAC, VAS and other clinical assessment are given below in table 1.

WOMAC scores for joint pain declined by 58.82% (mean ± SD: 66.43 ± 11.97 to 27.35 ± 7.92) at the end of 3 months (p< 0.0001). The reduction was significant from the 15th day itself (p = 0.02) and continued till day 90 as depicted in Figure 2.

Pain assessed by the patients using 10mm VAS was declined by 67.07% (mean ± SD: 7.11 ± 1.56 to 2.34 ± 0.72) at the end of 3 months (p< 0.0001). The reduction was significant from the 30th day itself (p = 0.005) and continued till day 90 as

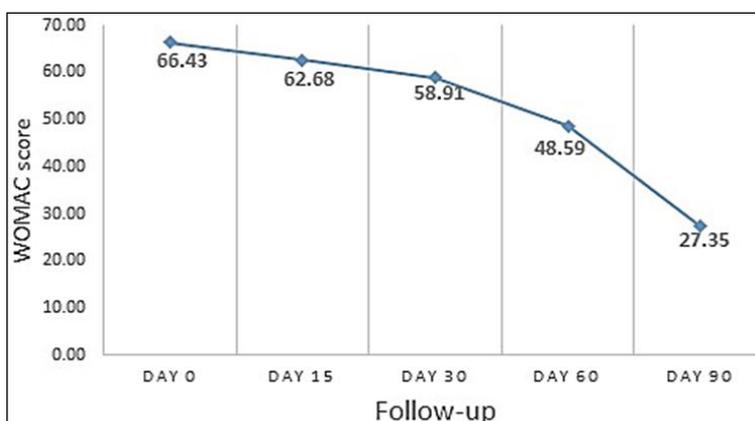
depicted in Figure 3.

Osteoarthritic symptoms such as palpation pain, limitation of mobility, joint crepitus, swelling and redness reduced in all patients after treatment with TriNyros (p< 0.01) as shown in table 1. Significant reduction in pain was observed from the 30th day itself (p< 0.001). There was significant reduction in palpation pain (82.98%) followed by redness (76.32%), swelling (59.26%) and joint crepitus (53.90%) as shown in Figure 4. There was less reduction in limitation of mobility (12.12%), yet it was significant (p< 0.01).

Table 1: Primary outcome measures at baseline and after 90 days of treatment with TriNyros

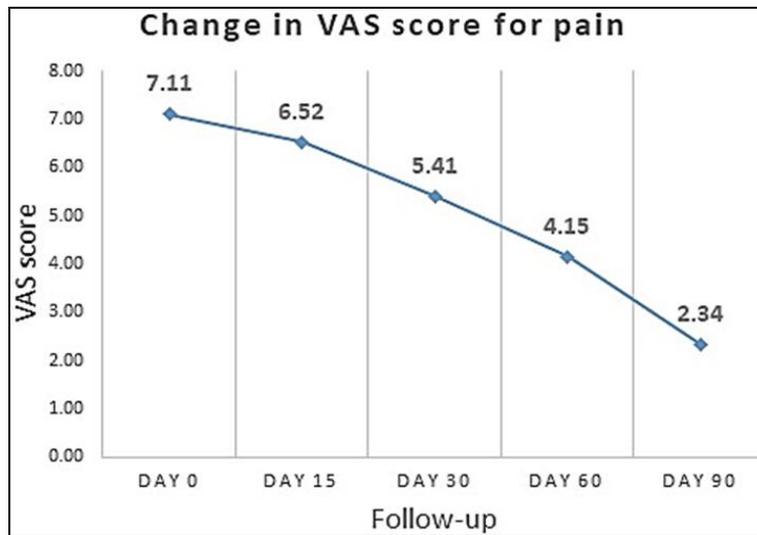
Sr. No.	Parameter	Before TriNyros (Day 0) (Mean ± S.D.)	After TriNyros (Day 90) (Mean ± S.D.)	% Change after 90 days of treatment
1.	Pain of Palpation	1.34±0.48	0.23±0.42	82.98% ^b
2.	Limitation of Mobility	0.94±0.23	0.83±0.38	12.12% ^a
3.	Joint Crepitus	1.34±0.63	0.62±0.80	53.90% ^b
4.	Swelling	1.03±0.56	0.42±0.50	59.26% ^b
5.	Redness	0.72±0.74	0.17±0.38	76.32% ^b
6.	WOMAC Score	66.43±11.97	27.35±7.92	58.82% ^b
7.	VAS Score	7.11±1.56	2.34±0.72	67.07% ^b

P< 0.01; P< 0.0001



Significant reduction in WOMAC score on day 15, 30, 60 and 90 (p< 0.05)

Fig 2: Reduction in WOMAC Score after treatment with TriNyros



Significant reduction in pain on day 15, 30, 60 and 90 ($p < 0.01$).
VAS: Visual Analogue Scale

Fig 3: Reduction in Pain assessed by visual analog scale (VAS) after treatment with TriNyros

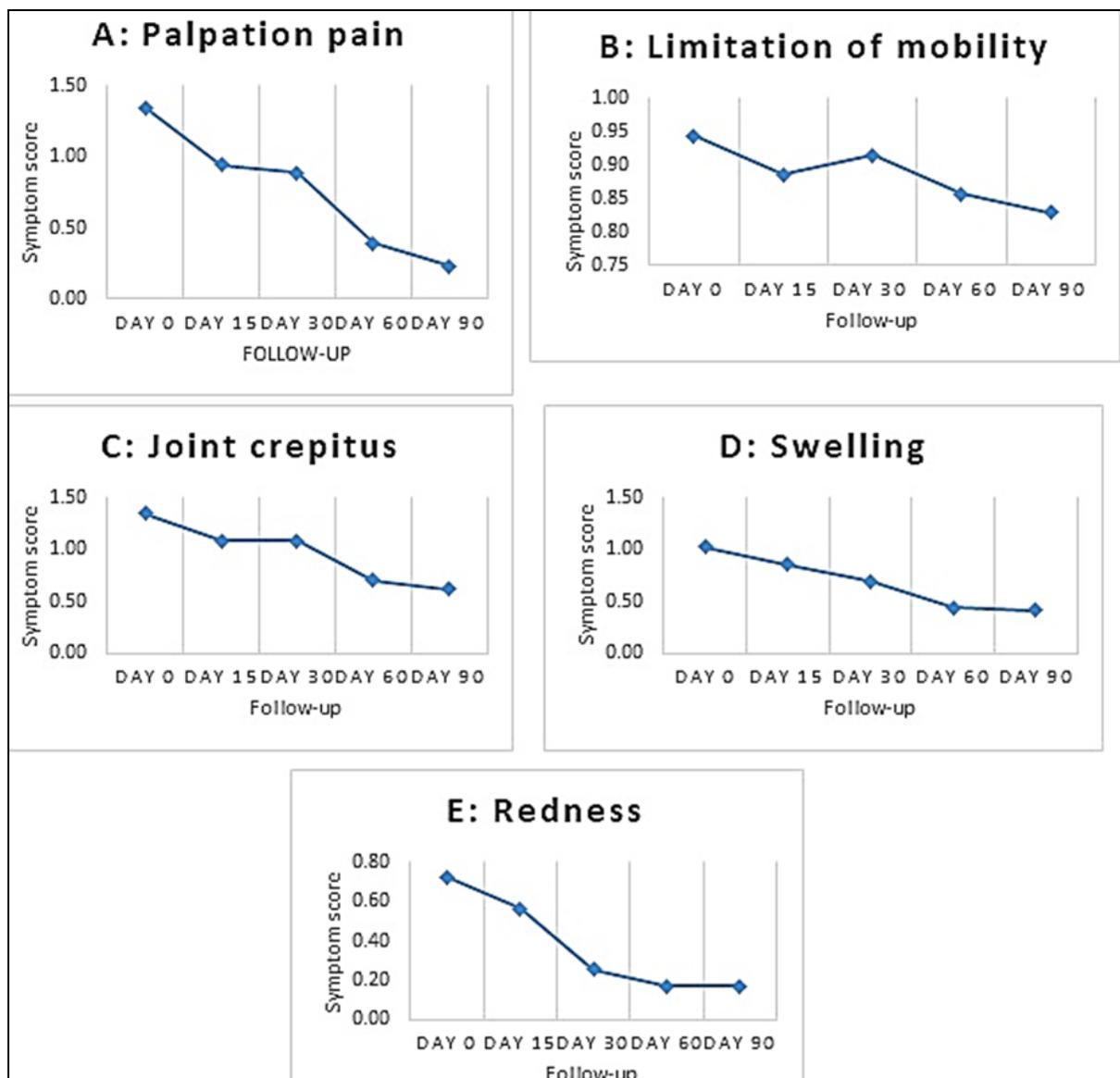


Fig 4: Change in clinical assessment scores of OA symptoms

Safety

ESR reduced significantly by 17.31% (20.80 ± 6.14 to 17.20 ± 5.72 mm/hr, $p < 0.05$). Lymphocytes significantly reduced by 44.93% ($P < 0.001$). There was no significant change in

other biomarkers or vitals (blood pressure, heart rate and respiratory rate). The data suggests that the treatment was safe and well tolerated in OA patients. No major adverse events were observed.

Discussion

This is the first clinical evidence generation program to evaluate the effectiveness and tolerability of TriNyros consisting of Rosehip, Aflapin® (AKBA) and IridoForce™ (harpagoside) in patients suffering from osteoarthritis of the knee. All patients reported significant reduction (mean = 58.82%, $p < 0.0001$) in WOMAC scores after 3 months of active treatment. Pain assessed by the patients was significantly reduced ($p < 0.0001$). Presumably these improvements might have occurred through down regulation of cartilage degrading enzymes (MMP-3) and anti-inflammatory action (inhibition of 5-LOX) as discussed earlier. Indeed, we were able to show that ESR reduced after treatment. Hematological and serum biochemical parameters remained unchanged. In addition, no major adverse effect were reported by the subjects. Taken together, these observations further demonstrate that TriNyros capsule is effective in reducing OA symptoms and improves WOMAC score.

Efficacy and safety of Boswellia and its extract in OA is well established in a meta-analysis of 28 clinical trials [27]. There exist only two clinical trials for Aflapin® in OA. The first clinical study involving Aflapin® was conducted in 40 subjects with OA of the knee who received either 100mg of Aflapin® or 100 mg of 5-Loxin or a placebo. Aflapin® exhibited better 5-lipoxygenase inhibitory activity, MMP-3 inhibition and oral bioavailability. WOMAC pain score reduced significantly [28]. The second study was a double-blind, randomized, placebo-controlled study that included 60 subjects with OA of the knee. The subjects received either 100 mg (n=30) of Aflapin® or placebo (n=30) daily for 30 days. Aflapin® provided significant improvements in pain and functional ability as early as the 5th day of treatment [29]. The safety of Aflapin® was tested using a battery of safety studies and it was found to be safe [30].

IridoForce™ is patented extract from the secondary roots (storage tubers) of Devil's Claw, due to higher content of harpagoside than its primary roots. A unique patented process allows IridoForce™ to offer an extract with the highest content of Harpagoside (up to 20% Harpagoside by HPLC or 40% by UV). In a review of 28 clinical trials of Devil's claw extracts, two high-quality studies (Lecomte *et al.* Chantre *et al.*) indicate that Devil's Claw was effective in reducing pain. Adverse events occurred at a very low rate of about 3%. Mainly mild gastrointestinal effects occurred and were similar with placebo. Long-term use of Devil's claw appears to be safe in the recommended dosage [31].

Dry powder of Rosehips exert anti-inflammatory properties through a reduction in CRP that started after 4 weeks of supplementation in patients with OA [32-36]. Rosehips have shown some efficacy in OA of the knee along with a counter reduction in the need of rescue medication [34]. It has a consistent, moderate efficacy in OA associated pain short-term clinical trials (3-4 months). Treatment with Rosehips seems safe to administer in humans as adverse events were similar to placebo in the available clinical studies [37].

Some limitations of BRATO should be considered. The program was not designed to evaluate concomitant or rescue medication since it was a post-marketing evidence generation program in the real world scenario to assess effectiveness and tolerability of add-on TriNyros to the existing treatment of knee OA. TriNyros was not compared with NSAIDs or other alternate therapies in this preliminary program. Further studies need to be undertaken to assess TriNyros associated reduction in rescue medication (NSAIDs) in knee OA. There

is a need of comparative evaluation between TriNyros and standard treatment. Structure-modifying variables as primary endpoints would help in determining chondroprotection action or disease-modifying property of TriNyros.

Conclusion

This is the first clinical evidence generation program that supports a potential use of TriNyros, a novel combination containing Aflapin®, Rosehip and IridoForce™ as an adjuvant in the management of OA of the knee. This novel combination has a multi-factorial mechanism of action that includes anti-inflammatory, antioxidant, analgesic and chondroprotective action. Aflapin, a constituent of TriNyros is an effective, safe and fast acting intervention in OA conferring significant improvement in pain and functional ability in as early as 5 days of treatment. The current study results also suggest the rapid onset of action and symptom resolution. TriNyros® decreased the pain and discomfort of knee osteoarthritis, improving the patient's general condition with no major adverse events. In the future, generating efficacy and safety data from a multicentric, randomized clinical trial comparing TriNyros and standard treatment options will be vital. Overall, TriNyros is indicated as an add-on therapy to NSAIDs in knee OA.

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