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Clinical efficacy of nutraceuticals in the management of osteoarthritis

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Abstract
Background: Osteoarthritis (OA) is a degenerative disorder affecting all joints & due to aphelia. The clinical manifestations of OA are swelling, pain & dysfunction of joints. Current non-pharmacological therapy mainly focuses on symptomatic treatment and may carry cardiovascular and gastrointestinal adverse effects. Nutraceuticals are preferred now a days owing to their safety and efficacy. TriNyros capsule consist of mixture of *Rosa canina* L. (Rosehip), *Boswellia serrata* and *Harpagophytum procumbens* (Devil`s claw) extract. These nutraceuticals are found to be effective as an anti-inflammatory, antioxidant, chondroprotective agent.
Aim: Current post marketing phase IV surveillance study was conducted to investigate the effectiveness of TriNyros capsule in OA patient with and without comorbidity.
Methods: Total 151 patients were enrolled in the study. All patients received cap. TriNyros containing [Rosehip 275 mg, IridoForce™ (Devil`s claw extract) 100 mg and Aflapin® 50 mg] twice daily for 90 days. Clinical assessment of symptoms included palpation tiredness, limitation of mobility, joint crepitus, swelling and redness. Osteoarthritis symptoms were measured using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Total European Quality of Life–5 Dimensions and visual analogue scale (VAS).
Results: After 90 day's treatment with Cap. TriNyros, WOMAC score reduced significantly from 39.62 + 11.95 to 13.36 + 4.82 ($p< 0.05$). In OA patients, both with & without comorbidity 66.12% & 66.57% reduction was observed respectively after treatment. For Total European Quality of Life–5 Dimensions (ED-5D) score, 72% improvement was observed after treatment with Cap. TriNyros. Similar improvement (69.83%) for Total ED-5D was observed in patient with comorbidity. Evaluation of clinical symptoms such as pain on palpation, limitation of mobility & joint crepitus was reduced significantly by 62.63%, 64.86%, & 69.46% respectively after TriNyros treatment. After 90 days, VAS score reduced from 6.41 $\pm$ 1.09 to 1.39 $\pm$ 0.78 (78.27%) in OA patient. No major adverse reactions were reported.
Conclusion: Current investigation revealed that TriNyros is effective in improving joint pain, WOMAC score and VAS score in OA patient with & without comorbidities.

Keywords: Osteoarthritis, aflapin, devils claw, anti-inflammatory, NSAIDs, cytokines etc

Introduction
Arthritis is an inflammation of the joint exemplified by swelling, pain, and restricted joint movement. Amongst, the various type of the arthritis most common is osteoarthritis (OA). Epidemiological data indicates that approximately 10-15% of the adults above 60 years of age demonstrate certain intensity of OA with higher prevalence in women than men. In Asian population, data shows that high prevalence of knee OA is observed especially in rural areas (13.7%) in comparison to urban areas (6.9%). In India, OA prevalence is higher in rural population (56.6%) than urban (32.6%). Due to changes in lifestyle Asian population are highly exposed to risk of knee osteoarthritis compared to Europeans and Americans [1, 2, 3].
The occurrence of OA is usually associated with synovial inflammation which is generally influenced by 5-lipoxygenase (5-LOX) pathway, proinflammatory cytokines and matrix metalloproteinases (MMP). These factors contribute to the enzymatic degeneration of cartilaginous matrix and leads to worsening the OA condition. Different treatment options such as use of drugs like NSAIDs and surgery can be considered for relieving pain from OA. However different study findings suggest that NSAIDs which are used to reduce the pain ultimately inhibit collagen matrix synthesis and thereby may cause more damage in OA.

Literature review for OA treatment suggest that nutraceuticals has become a viable option for treatment of OA due to its low side effects [4, 5, 6].

In recent years, interest in nutraceuticals such as Boswellia, Curcumin, Rose hip, aflapin, collagen peptide, ginger, glucosamine etc. is increasing owing to their strong ethnobotanical indication and identification as analgesic and anti-inflammatory action [7].

Nutraceutical formulations which include rose hip, devils claw and aflapin are popular due to their synergistic action in OA. Rose hip (berry fruits of *Rosa canina* L) contains different active ingredient such as GOPO (1,2-di-*O*-*α*-linolenoyl-3-*O*-*β*-d-galactopyranosyl-*sn*-glycerol), gallic acid, astragalin, turmeric acid etc. which plays important role in the treatment of rheumatoid arthritis. It shows causes reduction in pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), inhibit COX 1 & 2, reduces levels of C-reactive protein (CRP) [8].

Devils claw also known as *Harpagophytum procumbens* is a traditional African plant & it has been used as an anti-inflammatory agent in OA. It contains different acetylated phenolic glycosides, terpenoids and iridoid glycosides and primarily marketed as pain killer and anti-inflammatory agent in rheumatism and other joint disorders. IridoForce™ is the standardized extract of devils claw used in OA [9]. Aflapin is selective inhibitor of 5-LOX enzyme obtained from *Boswellia serrata* gum resin. It exerts its anti-inflammatory action by inhibition of 5-LOX & suppression of leukotrienes [10].

Table 1: Composition of TriNyros

Sr. No.	Constituents	Concentration
1.	Rosehip	275 mg
2	IridoForce™	100 mg
3	Aflapin®	50 mg

In current research, we evaluated the marketed product TriNyros (combination of Rosehip, IridoForce™, Aflapin) (Nutragenix Healthcare Pvt. Ltd.) (Table 1) as an additive treatment in OA patients and its effect in patients with & without comorbidity.

Methods

Study design

A phase IV post marketing surveillance study of Cap. TriNyros (Nutragenix Healthcare Pvt. Ltd.) was conducted at The Orthopaedic Speciality Clinic, Pune, Maharashtra from February 2021 till August 2021. The study protocol of Cap. TriNyros was duly approved by Ethics committee of Sahyadri Clinical Research & Development Center, Pune on 20th January 2021. All subjects who had signed written informed consent form before screening were enrolled and followed up-to three months.

Settings and participants

Patients were recruited from The Orthopaedic Specialty Clinic, Pune, Maharashtra aged between 19 to 75 years with the 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 had uncontrolled diabetes, hypertension, hepatic disorder, pregnant & lactating women, acute joint trauma of knee were excluded from the study.

Study intervention

During the study, the enrolled subjects were treated with TriNyros capsule [Rosehip 275 mg, Irido Force TM (Devil`s claw extract) 100 mg and Aflapin® 50 mg] twice daily for 3 months. All patients were advised not to consume other ayurvedic, herbal and homeopathic treatment during study period. The record of concomitant medication was maintained during study.

Outcome and follow up

At screening, baseline, day 15, 30, 60, and 90, data was obtained using standard case report forms. The primary objective was to evaluate the OA symptoms, WOMAC score, and Pain during the study. Pain on palpation, limited mobility, joint crepitus, edema, and redness were all graded on a 4-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe). The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index was used to quantify the severity of osteoarthritis symptoms, with a higher WOMAC score indicating more severe symptoms. The subjects rated their discomfort on a 10-mm visual analogue scale (VAS). At days 0, 15, 30, 60, and 90, the WOMAC, pain, and OA symptoms were evaluated. On day 90, the patient's global assessment and the physician's global assessment were to be evaluated.

Statistical 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.

Results

During the study total 151 patients were selected based on inclusion and exclusion criteria in which comprises 44 (29.14%) males and 107 (70.86%) females. The mean age of the subject was 56.80 years, and 71.52% patients belong to the age group above 50 years. Out of 151 patients, 78% patients had comorbidities such as hypertension, anxiety, diabetes mellitus, thyroid disorders etc. All the subjects selected during the study received TriNyros capsule two times daily for three months.

Primary outcome measures

1. WOMAC score

At the baseline the mean WOMAC combined score was 39.62 $\pm$ 11.95 ($p < 0.05$) which was reduced significantly to 13.36 $\pm$ 4.82 ($p < 0.05$) at the end of study. From the baseline 66.80% improvement observed in the patient after treatment with TriNyros (Figure 1).

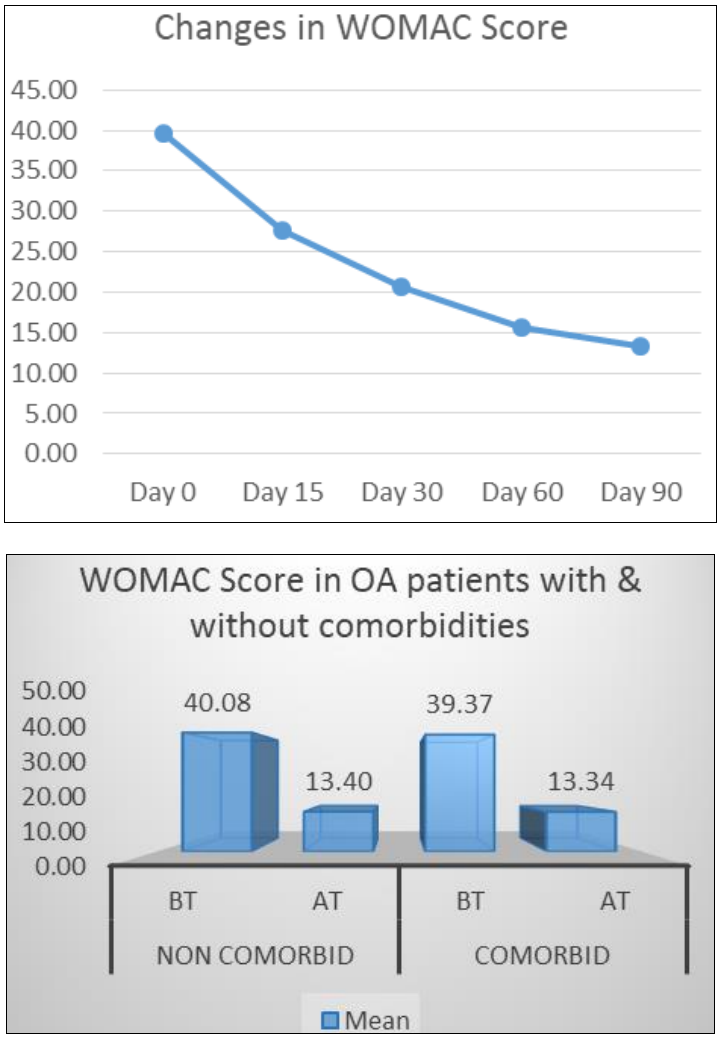
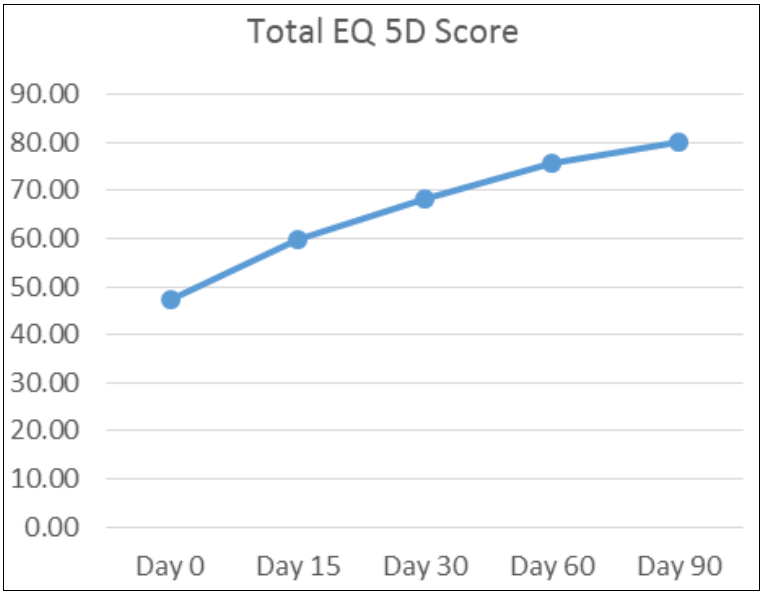


Fig 1: WOMAC score improvement after TriNyros treatment.

Further sub-group analysis shows that, total WOMAC score in OA patient with comorbidities reduced from 39.37 ± 11.52 to 13.34 ± 4.48 ($p < 0.05$) & in patient without comorbidities reduced from 40.08 ± 12.82 to 13.40 ± 5.43 ($p < 0.05$) after 90 days treatment with TriNyros. The change in effect was 66.12% & 66.57% in patients with and without co-morbidities respectively. The WOMAC score comparison shows that TriNyros shows similar changes in normal OA patients as well as in OA patients with co-morbidities. The improvement in WOMAC score of OA patient observed within 1 week after treatment with TriNyros.

2. Total European Quality of Life–5 Dimensions (EQ-5D) Score

After 90 days treatment with TriNyros, total ED-5D score significantly improved from 47.46 ± 8.10 to 81.64 ± 8.60 ($p < 0.05$). From the baseline, 72.01% improvement was observed in patients treated for three months (Figure 2).



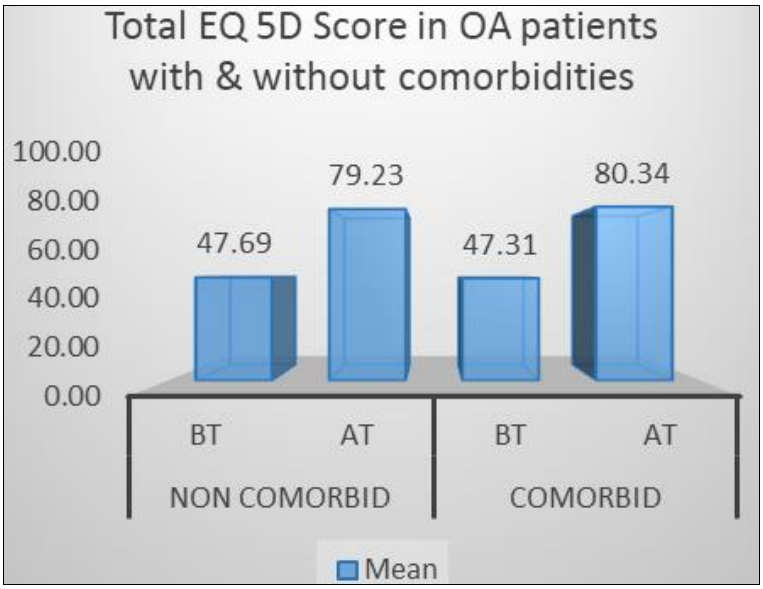


Fig 2: Total EQ-5D score in OA patient

In sub-group analysis, total EQ-5D score significantly improved from 47.31 ± 7.65 to 80.34 ± 14.45 ($p< 0.05$) in OA patients with co-morbidity and 47.69 ± 8.99 to 79.23 ± 14.60 ($p< 0.05$) in OA patients without co-morbidities. The% improvement in total EQ-5D score was found at 69.83% & 66.13% from baseline respectively in OA patient with comorbidity and without comorbidity.

2. Clinical symptoms score

During analysis of clinical symptoms parameters such as joint line tendinitis on palpations, limitation of mobility, joint crepitus, swelling and redness were included in the study. The treatment with TriNyros for 3 months leads to 62.63% reduction in pain on palpations of OA patient (Table 2). The subgroup analysis revealed that TriNyros reduces pain on palpations significantly from 1.98 ± 0.64 to 0.66 ± 0.52 (63.94%) in OA patient without any other disorder and 2.12 ± 0.63 to 0.77 ± 0.47 (66.67%) ($P< 0.05$) in OA patient with co-morbidities (Table 3).

After treatment with TriNyros, 64.86% improvement (reduction from 2.07 ± 0.63 to 0.73 ± 0.49) was observed in limitation of mobility (Table 2). Sub-group analysis revealed that 68.70% & 70.83% reduction in OA patient with comorbidity and without comorbidity respectively (Table 3).

Table 2: Clinical symptoms score at baseline and 90 days treatment with TriNyros

Sr. No.	Parameters	Before TriNyros at baseline (Mean ± SD)	After TriNyros at Day 90 (Mean + SD	% Change after 90 days of treatment
1	Pain on Palpations	1.97 ± 0.69	0.74 ± 00.46	62.63%
2	Limitation of Mobility	2.07 ± 0.63	0.73 ± 0.49	64.86%
3	Joint Crepitus	1.34 ± 0.63	0.41 ± 0.52	69.46%
4	Swelling	1.44 ± 0.68	0.24 ± 0.43	83.41%
5	Redness	0.69 ± 0.59	0. 09 ± 0.28	87.50%

Movement of a joint affected by OA may cause a crackling or grating sensation called "crepitus".

OA treatment with TriNyros for 90 days, reduces joint crepitus from 1.34 ± 0.63 to 0.41 ± 0.52 (69.46%) (Table 2). The reduction rate for joint crepitus is similar in OA patient with comorbidity (70.83%) & without comorbidity (68.70%) (Table 3).

Table 3: Clinical symptoms score changes in OA patient with comorbidity and without comorbidity after treatment with TriNyros

Sr. No.	Parameters	At baseline	After 90 days	% Change after 90 days of treatment	Significance
1	**Pain on Palpation**				
	With comorbidity	1.98 ± 0.69	0.72 ± 0.47	63.40%	
	Without comorbidity	1.94 ± 0.69	0.75 ± 0.43	61.17%	
2	**Limitation of mobility**				
	With comorbidity	2.12 ± 0.63	0.77 ± 0.47	63.94%	
	Without comorbidity	1.98 ± 0.64	0.66 ± 0.52	66.67%	
3	**Joint crepitus**				
	With comorbidity	1.34 ± 0.61	0.42 ± 0.54	68.70%	$P< 0.05$
	Without comorbidity	1.36 ± 0.68	0.40 ± 0.49	70.83%	
4	**Swelling**				
	With comorbidity	1.44 ± 0.67	0.22 ± 0.45	84.40%	
	Without comorbidity	1.43 ± 0.69	0.26 ± 0.45	81.58%	
5	**Redness**				
	With comorbidity	0.74 ± 0.55	0.08 ± 0.28	88.89%	
	Without comorbidity	0.60 ± 0.66	0.09 ± 0.30	84.38%	

OA usually occur in elderly patient which causes wearing down of the cartilage and leads to joint swelling and redness. After treatment with TriNyros, swelling and redness reduced from 1.44 ± 0.68 to 0.24 ± 0.43 (83.41%) and 0.69 ± 0.59 to 0.09 ± 0.28 (87.50%) respectively (Table 2). During the study, swelling improved by 84% and redness improved by 88.89% from baseline after treatment in patients with co-morbidity (Table 3).

Secondary outcome measures

1. VAS score

VAS score is generally used to determine the intensity of pain in patient. TriNyros treatment reduces VAS score from 6.41 ± 1.09 to 1.39 ± 0.78 (78.27%) after 90 days in OA patient (figure 3). Furthermore, sub-analysis evaluation revealed that 79.37% & 76.15% reduction observed respectively in patient with and without comorbidity (figure 3). The changes in VAS score is observed after 1 week of treatment with TriNyros.

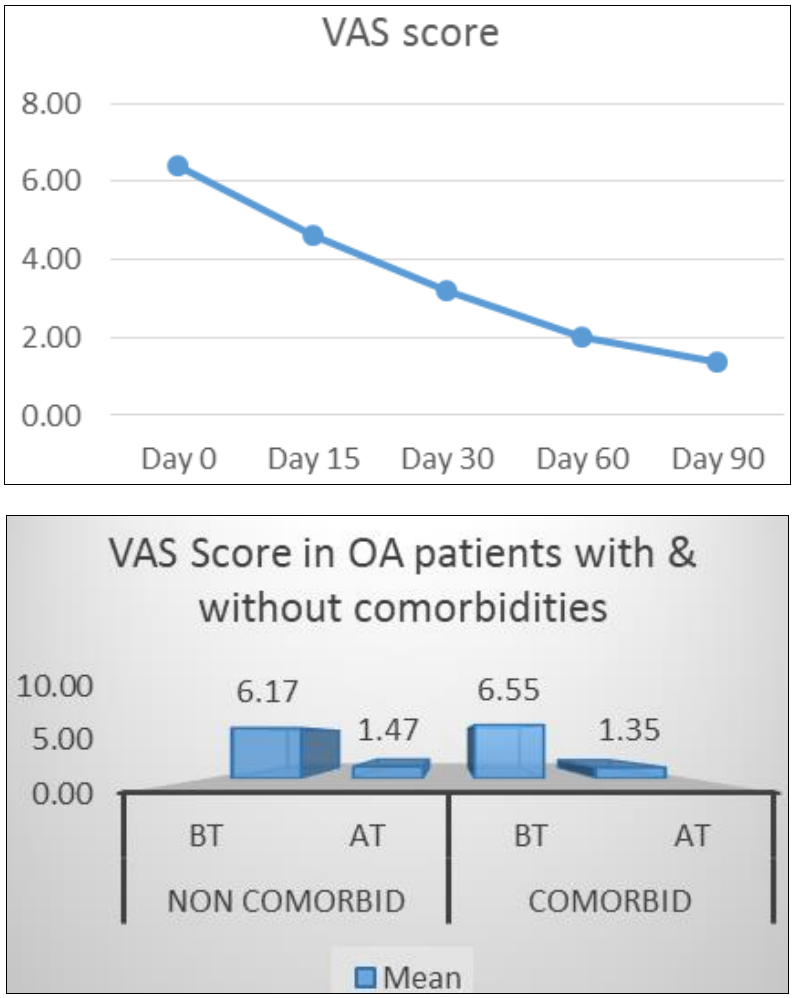


Fig 3: VAS score in OA patient after treatment with TriNyros for 90 days

2. Patient & Physician global assessment

The patient & physician global assessment of osteoarthritis activity is vital component of various measures of disease activity. During three-month, 92.05% of OA patients as well as physicians were satisfied with TriNyros treatment. No patients and physician reported any non-compliance with TriNyros during the study.

Discussion

This phase IV post surveillance study investigated the clinical efficacy of TriNyros in patients with osteoarthritis We found that administration of TriNyros for three months leads to improvement in WOMAC score, Total EQ-5D score, VAS score, pain on palpation, limitation of mobility, joint crepitus, swelling and redness in OA patient. Further subgroup analysis revealed that, TriNyros shows similar efficacy in OA patient with & without comorbidity. The improvement in OA was observed in early 1st week after initiation of treatment with TriNyros. Patient and physician global assessment revealed that TriNyros is highly accepted and shows no non-compliance during the study. The results obtained in the current study are in line with the previously published study performed by Anand *et al*. (2020) [11]. In the previous study 58.82% reduction in WOMAC score, & 67% reduction in VAS score was observed in OA patient treated with TriNyros for 90 days [11].

Osteoarthritis is a progressive disability disorder that affects 10 to 15% of the Indian population above 60 years. However, age is a key risk factor. Osteoarthritis treatment possess a huge cost with the restrictions in physical performance and discomfort [12]. Despite this burden and the high prevalence of osteoarthritis, little has been done to alter the disease's course and ameliorate symptoms. The current conventional treatment is nonsteroidal anti-inflammatory drugs (NSAIDs), which relieve symptoms such as pain but do not change the course of cartilage loss and joint degeneration. Furthermore, NSAIDs are linked to a high prevalence of gastrointestinal, cardiovascular, and renal adverse effects, all of which are potentially lethal [12, 13].

Innovations that provide symptomatic relief as well as change

the course of the disease are desperately needed, and nutraceutical techniques have piqued interest as an alternative to pharmacological approaches. TriNyros is the mixture of *Rosa canina* L. (Rosehip), Boswellia serrata and Harpagophytum procumbens (Devil`s claw) extract, which are most commonly referred in traditional herbal system. Oral administration of *Rosa canina* L. for three months significantly reduced WOMAC score & stiffness in OA patients. It also reduced the consumption of rescue medication required during OA treatment [14]. The use of Rose hip powder for 4 weeks also found to be effective in reducing blood CRP levels and exert its anti-inflammatory action in arthritis patient [15, 16].

Bosewellia serrata extract consist of 3-O-Acetyl-11-keto-beta-boswellic acid (AKBA) which contribute to its anti-inflammatory action by inhibiting 5-lipoxygenase. Aflapin is a novel composition derived from Bosewellia serrata and Vishal AA *et al*. 2011 shows that it is more effective in alleviating pain, joint stiffness and improves physical functioning of patients with OA [17]. The meta-analysis of 28 studies revealed that Bosewellia serrata extract are safe and effective in OA patient [18].

IridoForce™ is a trademarked extract from Devil's Claw's secondary roots (storage tubers), which contain more harpagoside than the primary roots. IridoForce™ is able to provide an extract with the highest concentration of Harpagoside thanks to a patented technique (up to 20 percent Harpagoside by HPLC or 40 percent by UV). Two high-quality studies (Lecomte *et al*. and Chantre *et al*.) found that Devil's Claw extracts were effective in reducing pain in a review of 28 clinical trials. Adverse events were reported at a very low rate of around 3%. Mainly mild gastrointestinal symptoms occurred and were similar with placebo. In the approved dosage, long-term usage of Devil's claw looks to be safe [19, 20].

There are some limitations of the current study. To begin, no established drugs, such as NSAIDs, were used to evaluate the effects of TriNyros to standard treatment. Secondly parameters such as body weight & body mass index (BMI) are not considered during the study. Obesity is important factor in the symptomatic OA as it has an important effect on the treatment. Finally, only one fixed dose of TriNyros was used during the study to evaluate its efficacy; hence we could not validate effect of different doses on safety and efficacy in OA patient. Further clinical trials with larger sample numbers and varied dosages are needed to establish safety and efficacy.

Conclusion

The findings of the current phase IV post marketing surveillance suggest that TriNyros (Nutragenix Healthcare Pvt. Ltd) act synergistically to exert anti-inflammatory/anti-arthritic activity. Cap TriNyros efficaciously reduces joint pain and improves the physical functional ability of OA patient. Furthermore, Cap. TriNyros shows similar efficacy in OA patients with comorbidity and without comorbidity.

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