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Role of Rosehip, Devil's claw, and *Boswellia serrata* in osteoarthritis: Molecular and clinical perspectives

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Abstract
Osteoarthritis (OA) is a degenerative joint disease orchestrated by various-signal transduction pathways working together in the joint, ultimately causing an imbalance between the catabolic and anabolic processes. These pathways are responsible for inflammation, leading to pain and disability. Nonsteroidal anti-inflammatory drugs (NSAIDs) carry the risk of cardiovascular and gastrointestinal side effects, for which alternative drug treatment has become popular. The ideal therapy should modify osteoarthritis's natural history and alter the destructive process of articular cartilage without concerning side effects. Nutraceuticals from natural sources help balance anabolic and catabolic processes in the joint tissue and improve redox balance, thus providing cartilage protection. Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata* exert active effects on various OA targets such as inflammation and catabolism, suppress oxidative stress, relieve chronic pain, and exert complementary, additive and synergistic anti-arthritic effects. The safety of Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata* alone and in combination is well established. The recent clinical evidence suggests the potential promise in favour of this combination as a proper initial therapeutic strategy for arthritis management.

Keywords: Osteoarthritis, Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata*

Introduction

Osteoarthritis-Epidemiology

Osteoarthritis (OA) is a common chronic inflammatory degenerative disease affecting 7% of the global population, with women inexplicably affected by the condition [1, 2]. Around 63 million people in India had OA in 2019. The age-standardized prevalence of OA increased from 4,895 in 1990 to 5313 in 2019 per 100,000 persons. OA-associated Disability-adjusted life years (DALYs) was 2.12 million in 2019 [3].

The most prevalent risk factors of primary OA are aging, genetic predisposition, sociodemographic characteristics, and diet-related factors [1]. In clinical practice, the knee is the most frequent OA site, followed by the hand and hip. Knee OA stands for 85% of the OA burden worldwide [2].

Pathophysiology of osteoarthritis

OA is not just simply a degenerative "wear and tear" of the cartilage but rather OA is the abnormal remodelling of joint tissues driven by multiple-signal transduction pathways producing inflammatory mediators within the affected joint [4]. OA is characterized by articular and meniscal cartilage damage, sclerosis of subchondral bone, osteophytes, and synovial tissue inflammation. Pro-inflammatory cytokines such as IL-1β, tumor necrosis factor (TNF)-α, and IL-6 and several other proteases, such as matrix metalloproteinases 3, 9, and 13 (MMP-3, MMP-9, MMP-13), tartrate-resistant acid phosphatase (TRAP), or metalloproteinase with thrombospondin Motifs (ADAMTS) are critical facilitators of cartilage degeneration and synovium inflammation [5, 6]. Oxidative stress observed in OA cartilage and chondrocytes also plays an important role in the remodeling of joint tissues [7].

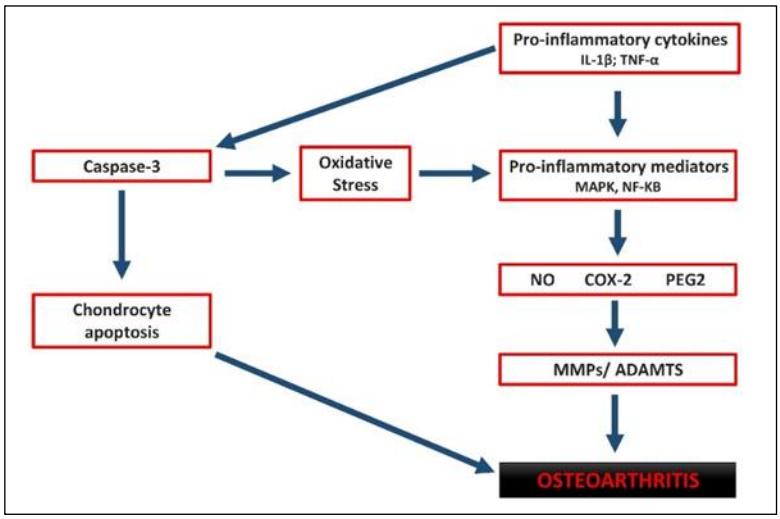

Fig 1: Molecular pathogenesis of OA

Limitations of current pharmacological treatments

As there is no cure for OA, most pharmacological agents emphasize alleviating pain and improving joint function. NSAIDs need to address the evolving and intricate nature of OA. NSAID use can lead to gastrointestinal, renal, and cardiovascular complications. Hence there is an urgent need for OA disease-modifying remedies which not only improve symptoms and modify the disease progression but also have long-term safety [8].

Nutraceuticals from natural sources for OA

Nutraceuticals—food or food products (Phyto flavonoids, polyphenols, and bioflavonoids found in plant parts) are safe alternatives to current pharmacologic therapies. Owing to their anti-inflammatory, anti-catabolic, and antioxidant action, natural products can exert disease modification in OA. Around 47 % of adults use non-prescribed alternative medications for OA treatment [8].

1) Role of Rosehip extract in osteoarthritis

The genus Rosa L. belongs to the family Rosaceae, which encompasses over 100 species scattered widely in Europe, Asia, the Middle East, and North America. Rose hip is the fruit of the Rosa plant, and fruits from Rosa canina L. are marketed as an essential food source used as a traditional medicine in several cultures [9].

Standardised rosehip powder has antioxidant activity, inhibits NF-B signalling and pro-inflammatory enzymes, downregulates inflammatory cytokine and chemokine production, and lowers C reactive protein levels. The anti-inflammatory action of standardised rosehip powder is mainly due to its constituents like galactolipids (2S)-1, 2-di-O-[(9Z, 12Z, 15Z)-octadeca-9, 12, 15-trienoyl]-3-O-ß-D-galactopyranosyl glycerol (GOPO).

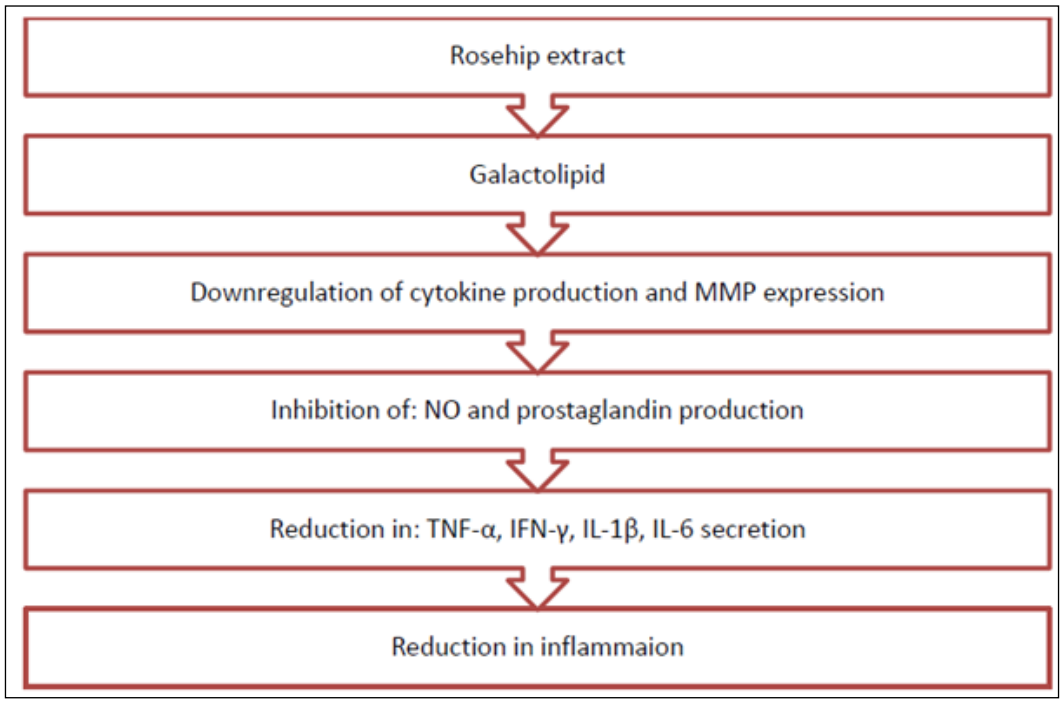

Fig 2: Antiinflammatory action of Rosehip

Other actions of rosehip extract include Antidiabetic, lipid-lowering, and anti-obesogenic activity [11, 12]. Multimodal steps of rosehip extract in OA are shown in figure 3 [13].

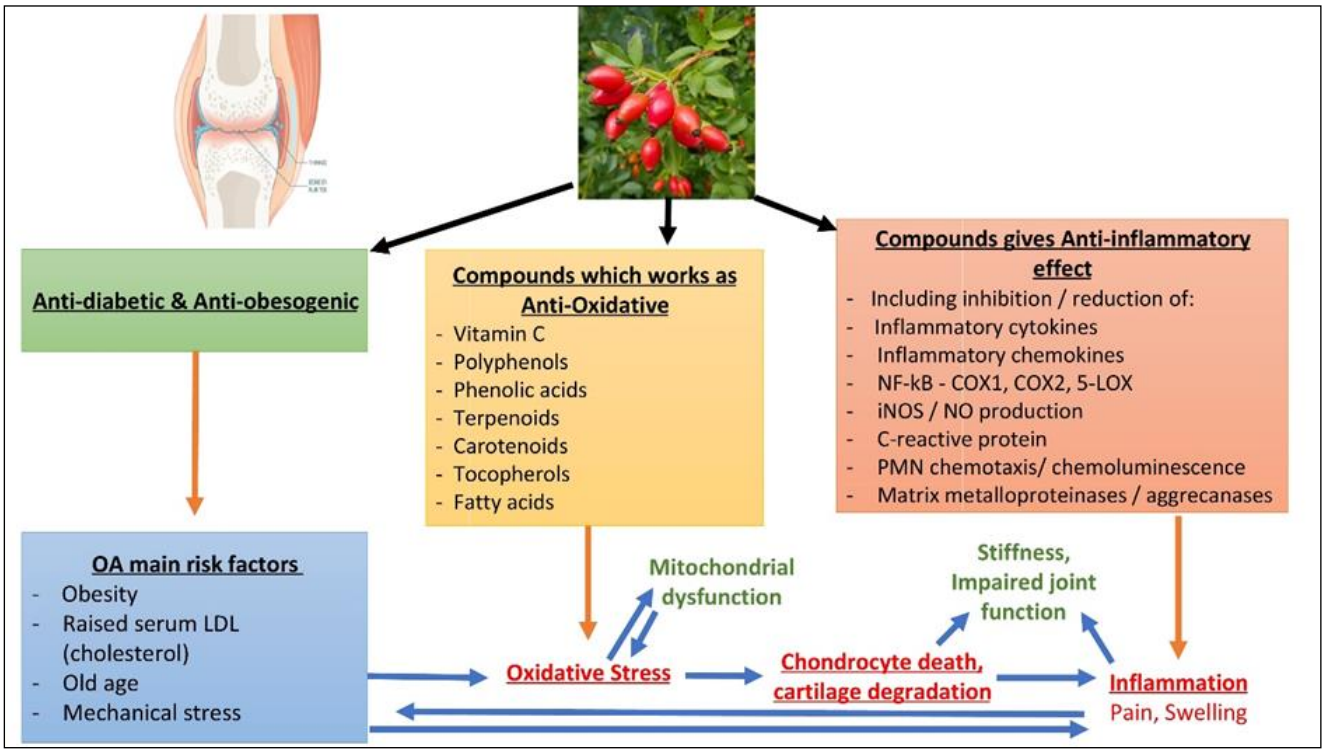

Fig 3: Multimodal actions of rosehip extract in OA

Clinical Evidence

In the past two decades, numerous research papers have elucidated the clinical benefits of standardised rosehip powder in the management of OA. The rosehip extract alleviated joint pain, stiffness, and mobility in most studies without producing side effect.

Table 1: Clinical evidences for effect of rosehip extract in osteoarthritis

Author/year	Dosage	Result	Conclusion
O. Warholm 2003 (14)	Group 1: Five 0.5g capsules of standardized rose-hip powder twice daily for 4 months (n=50) Group 2: Placebo twice daily for 4 months (n=50)	Compared to the placebo, the hip joint mobility improved significantly (P = 0.033) and pain decreased significantly in the rosehip group (P = 0.035).	Standardized rosehip powder causes improvement in hip flexion and decreases pain in OA patients.
E. Rein 2004(15)	N=112 Patients Group 1: Placebo 5 g daily for 3 months then wash off period after that Rosehip extract therapy 5g daily for 3 months Group 2: Rosehip extract 5 g daily for 3 months then wash off period after that therapy continue with Placebo 5g daily for 3 months	After 3 months, rosehip showed significant reduction in joint pain in 66% of the patients compared to 36% of placebo-treated patients ($p < 0.0185$) No major side effects reported in any group.	The Rosehip extract reduces the symptoms of osteoarthritis.
K Winther 2005(16)	47 patients were treated with 5 g of rosehip powder daily for 3 months and the remaining patients were given placebo for same duration. The crossover was done for next 3 months.	Compared to the placebo, Rose-hip caused a significant decrease in WOMAC (Western Ontario and McMaster Universities Arthritis Index) pain ($p<0.014$) after 3 weeks of treatment. The intake of 'rescue medication' significantly reduced with rosehip treatment ($p<0.027$).	Rosehip can reduce symptoms of osteoarthritis and can reduce the utilization of salvage medication.
R. Christensen 2014(17)	Treatment A: Original rosehip powder (4.5g) +vitamin C (80 mg) once daily (n=49) Treatment B: enhanced rosehip powder, (4.5g) of the new seedless rosehip powder + vitamin C (80 mg)once daily(n=50) Treatment C: Enhanced rosehip powder (2.25 g)of the new seedless rosehip powder + vitamin C (80 mg)once daily (n=51)	Pain during walking decreased during the trial period (12 weeks); the pain reduction was comparable across groups. Changes in the Knee Injury and OA Outcome Score symptoms showed the potential superiority of enhanced rosehip powder versus original rosehip powder	Enhanced rosehip powder was at least as good, even in less dose as compared to the original rosehip product.
S. Mahajan 2020(18)	Group 1: Rosehip powder 750 mg 2 capsules BD for 3 months + Paracetamol 650 mg BD.(n=35) Group 2: Placebo BD for 3 months +Paracetamol 650 mg BD. (n=40)	More improvement in joint pain, stiffness and physical function was observed in Rosehip group patients as compared to placebo group patients ($p<0/001$) Both treatments were generally well tolerated.	As an adjuvant, rose hip extract produces better effects than the placebo.

Safety

Rosehips from different Rosa species have been widely used in traditional folk medicine for years. Rosehip powder is generally deemed to be safe. Occasional allergic reactions or gastrointestinal complaints are seen but serious adverse effects have not been observed. Rosehip use during pregnancy and lactation is not recommended as there is a lack of data about its safety [19].

2) Role of Devil's claw (*Harpagophytum procumbens*) in osteoarthritis

Harpagophytum procumbent (Devil's claw) is a popular medicinal plant found mainly in southern Africa. Devil's claw has several bioactive components like terpenoids, harpagoside and harpagide, and iridoid glycoside bioactive compounds which have anti-inflammatory and anti-analgesic activity [20]. Harpagoside exerts its anti-inflammatory effects by inhibiting COX-1 and COX-2 enzymes and the downregulation of pro-inflammatory cytokines and NO production. In human OA chondrocytes, anti-inflammatory activity via c-Fos/AP-1 signal suppression. It has been shown to mediate anti-Inflammatory effects in Osteoarthritis synoviocytes through cannabinoid type 2 (CB2) Activation. *Harpagophytum procumbens* is able to inhibit the cAMP production and mitogen-activated protein (MAP) kinase activation and to down-regulate the matrix metalloproteinase (MMP-13) production which is the hallmark of osteoarthritis [21].

Clinical Evidence

Various preparations from H. Procumbens have been used in Europe for over half a century and have become an established traditional treatment for arthritis complaints. European Scientific Cooperative on Phytotherapy (ESCOP) recommends Devil's claw preparations for osteoarthritis and low back pain. Recent studies indicated that preparation from *Harpagophytum procumbens* is effective in the case of OA.

Table 2: Clinical evidence for the effect of *Harpagophytum procumbens* extract in osteoarthritis

Author/year	Dosage	Result	Conclusion
P. Chantre 2000 [22]	*Harpagophytum procumbens* Group: 435 mg *Harpagophytum procumbens* for 4 months (n=62) Diacerein Group: Diacerein 100 mg/day for 4 months(n=60)	Both therapies were equiefficacious in improving spontaneous pain, reducing the Lequesne functional index. Patients on *Harpagophytum procumbens* had significantly less use of painkiller. The frequency of side effects was significantly lower in the *Harpagophytum procumbens* group	*Harpagophytum procumbens* is equiefficacious to diacerein and has superior safety profile compared to diacerein.
Lecomte 1992 [23]	H group: 2000 mg/day (Harpagoside content estimated indirectly as 60 mg per day) P Group: Placebo for 60 days	Mean pain improvement: H=38%, P=25% (p<.05) finger-ground distance modified Schober test (cm) mean improvement: H=16%, P=6% (p<.05) None of the groups showed any adverse drug reactions.	*Harpagophytum procumbens* is better than a placebo.
Hamid Reza Farpour 2021 [24]	Group A: Daily administration of two *Harpagophytum procumbens* tablets (2 ∗ 480 mg) for one month Group B: Daily administration of 15 mg of meloxicam for ten days	Visual analog scale (VAS), Oxford Knee Scale (OKS), and WOMAC scores improved in both groups (p < 0.001) over time, but there was no significant difference between the groups.	*Harpagophytum procumbens* is an effective and safe treatment in patients with mild Knee OA.

Safety

Products containing *Harpagophytum procumbens* have been registered as traditional herbal medicinal products. The therapeutic use of devil's claw has been documented in several medicinal handbooks for at least 30 years. Harpagophytum root preparations were generally well tolerated. The most commonly reported side effects, when all clinical studies are taken into consideration, are mild gastrointestinal complaints (nausea, abdominal pain, diarrhoea) and allergic skin reactions. Use of *Harpagophytum procumbens* is not recommended during the pregnancy and lactation because of lack of safety data [25].

3) Role of *Boswellia serrata* in osteoarthritis

Boswellia is derived from the gum resin extracts of the Indian olibanum tree, *Boswellia serrata*, which contains a mixture of triterpene acids known as Boswellia acids [26]. 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid mediate the anti-inflammatory effects of *Boswellia serrata*. Boswellic acids inhibit the 5-Lipoxygenase (5-LOX) pathway, reducing the production of proinflammatory leukotrienes and decrease mRNA expression of MMPs and cyclooxygenase-2, prostaglandin E2, and pro-inflammatory cytokines. *Boswellia serrata* treatment can directly stopped chondrocyte cell death [27].

Clinical Evidence

Various clinical studies have shown that *Boswellia serrata* extract (BSE) improves pain and physical functions in OA patients [28–30].

Table 3: Clinical evidence for the effect of *Boswellia serrata* extract in osteoarthritis

Author/year	Dosage	Result	Conclusion
Kimmatkar N 2003 [28]	Group A: 333mg of BSE capsule three times a day for eight weeks (n=15) Group B: Placebo capsule three times a day for eight weeks (n=15)	Compared to the placebo all the patients receiving BSE treatment reported a statistically significant decrease in knee pain. BSE was well tolerated by the patients.	BSE is recommended in patients with OA knee.
Krishanu Sengupta, 2008 [29]	Group 1: 100 mg of novel *Boswellia serrata* extract daily for 90 days (n=25) Group 2: 250 mg of novel *Boswellia serrata* extract daily for 90 days (n=25) Group 3: Placebo for 90 days (n=25)	Compared to placebo, *Boswellia serrata* extract caused statistically significant and clinically significant improvement in pain and physical function scores in OA patients.	*Boswellia serrata* extract improves joint health by reducing cartilage degradation in OA patients.
Alluri V. Krishnaraju 2010 [30]	Group 1: 100 mg of novel B. serrata extract daily for 90 days (n=20) Group 2: 100 mg of Aflapin (novel synergistic	B. Serrata lead to clinically and statistically significant improvements in pain scores and physical function	*Boswellia serrata* extract is efficacious and safe and tolerable

	composition containing B. serrata extract selectively enriched with 3-O-Acetyl-11-keto-β-boswellic acid and B. serrata non-volatile oi daily for 90 days (n=20) Group 3: Placebo for 90 days (n=20)	scores in OA subjects and side effects were comparable to placebo	in subjects with OA

**Safety **

B. Serrata has a long history of traditional use and is conferred the status of GRAS (Generally Recognized as Safe) by the US Food and Drug Administration. The use of B. Serrata is not recommended in pregnancy and lactation because of the lack of safety data in this population [27].

4) Combinations of Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata*

Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata* can be novel nutraceutical-based compound formulations that "shoot" many OA molecular targets and be a novel therapeutic strategy for a new generation of nutraceuticals in OA prevention and treatment.

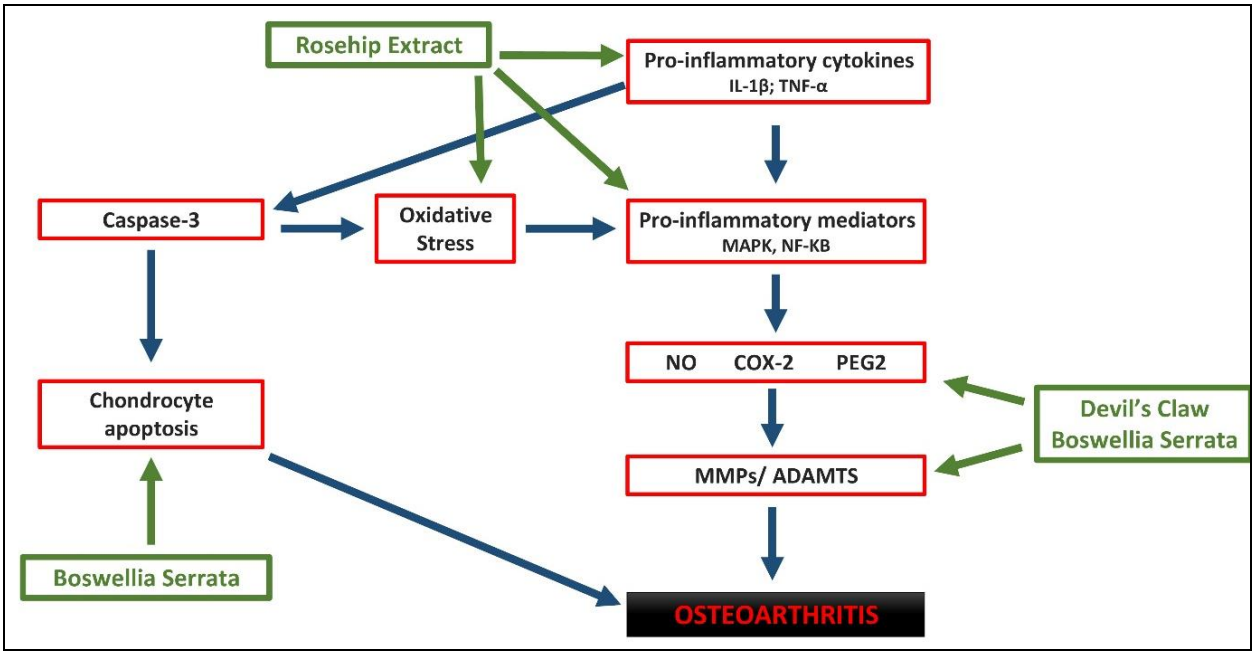

Fig 4: Mechanism of Combinations of Rosehip extract, *Harpagophytum procumbens* and *Boswellia serrata*

Clinical Evidence for the effectiveness of combination in OA patients

The summarised evidence shows that a combination of rosehip, *Boswellia serrata* and *Harpagophytum procumbens* provides the better effect in OA.

Table 4: Clinical evidence for the effect of combination (Rosehip extract, Devil's claw extract and *Boswellia serrata* extract) in osteoarthritis

Author	Dosage	Result	Conclusion
Gautam Chakravarty (2020) [31]	Rosehip extract 275 mg, devil's claw 100 mg, Boswellia extract 50 mg) twice daily for 90 days	Combination therapy lead to a significant reduction in WOMAC scores and was seen in the majority of the patients at day 15, 30, 60, and 90 (p<0.0001). Pain measured by VAS significantly reduced by 67% (p<0.0001) at days 30, 60, and 90.	Rosehip combination was found to be effective and well-tolerated in decreasing pain and upgrading general conditions in OA patients
Gautam Sinha (2021) [32]	2 groups of 30 patients each, Group A received an oral tablet containing a combination of Rosehip extract 275mg, *Boswellia serrata* extract 307.5mg, and Devil's claw extract 100mg for 90 days Group B received an oral tablet containing Diacerein 50mg for 90 days	Both treatments were equi-efficacious in reducing the WOMAC score.	The oral drug containing a combination of Rosehip extract, *Boswellia serrata* extract, and Devil's claw extract is effective and safe in easing symptoms of OA knee
Sachin Tapasvi (2022) [33]	Rosehip extract 275 mg, Devil's claw 100 mg, Boswellia extract 50 mg) twice a daily for 90 days in every patient	WOMAC score reduced significantly from 39.62 ± 11.95 to 13.36 ± 4.82 (p< 0.05). Evaluation of clinical symptoms such as pain on palpation, limitation of mobility & joint crepitus were reduced significantly by 62.63%, 64.86%, & 69.46% respectively after treatment.	Current investigation revealed that the rosehip combination is effective in improving joint pain, WOMAC score, and VAS score in OA patients with & without comorbidities.
Sanjay Kumar Gupta (2022) [34]	Rosehip extract 275 mg, Devil's claw 100 mg, Aflapin 50 mg twice a daily for 90 days in every patient	Treatment with rosehip combination for 3 months leads to 60.64% reduction in pain on palpations of OA patient The reduction rate for joint crepitus is similar in OA patients with comorbidity (72.65%) & without comorbidity (66.70%).	Rosehip combination efficaciously reduces joint pain and improves the physical functional ability of OA patients.
Varun Kumar	Rosehip extract 275 mg, Devil's claw	Treatment with a rosehip combination for 3 months	Capsule rosehip combination

(2022) [35]	100 mg, Aflapin 50 mg twice a daily for 90 days in every patient	leads to a 60.64% reduction in pain on palpations of OA patient The reduction rate for joint crepitus is similar in OA patients with comorbidity (72.65%) & without comorbidity (66.70%).	efficaciously reduces joint pain and improves the physical functional ability of OA patients.

Safety

There was no significant change in other biomarkers or vitals (blood pressure, heart rate, and respiratory rate). The data suggest that the treatment was safe and well tolerated in OA patients. No significant adverse events were observed [32].

Conclusion

OA is a multifactorial disease characterised by the progressive destruction of joint cartilage tissue, pain and inflammation, stiffness, and impaired physical activity. The efficacy of using an individual compound to treat a complex and chronic disease with multiple risk factors, such as OA, may be limited. Hence nutraceutical-based approaches may require a combination of compounds like Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata*, which exert dynamic effects on OA targets such as inflammation and catabolism, suppress oxidative stress and relieve chronic pain, as well as exercise complementary, additive, and synergistic anti-arthritic effects. The safety of Rosehip extract, *Harpagophytum procumbens*, and *Boswellia serrata* alone and in combination is well established. Cap Combination efficaciously reduces joint pain and improves the physical functional ability of OA patients. The recent clinical evidence suggests the potential promise in favour of this combination as a sound initial therapeutic strategy for arthritis management.

Conflict of Interest

Not available

Financial Support

Not available

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