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Original Research Article

Pain Reduction in Knee Osteoarthritis: A Prospective Study Comparing Boswellia Serrata and Eggshell Membrane Supplementation

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Conflict of interest: Nil

Abstract

Background: Osteoarthritis (OA) is a prevalent musculoskeletal disorder characterized by joint pain and functional impairment. Traditional therapies often involve NSAIDs, which can cause adverse effects. Natural alternatives such as Boswellia serrata (BS) and Natural Eggshell Membrane (NEM) are emerging as potential treatments with fewer side effects.

Aim: To compare the efficacy of Boswellia serrata and Natural Eggshell Membrane in reducing pain in patients with knee OA.

Methods: Prospective, observational study was conducted at King George's Medical University, Lucknow, over 18 months. A total of 117 patients were divided into three groups: Group A received Etoricoxib alone, Group B received Etoricoxib with NEM (Natural egg shell membrane), and Group C received Etoricoxib with BS (Boswellia serrata). Pain levels were assessed using the Visual Analogue Scale (VAS) at baseline, 60 days, and 120 days. Statistical analyses were performed using SPSS version 26.

Results: All groups showed significant reductions in VAS scores over time ($p<0.001$). The greatest pain reduction was observed in Group C (BS), followed by Group B (NEM), with Group A showing the least improvement. Intergroup analysis showed statistically significant differences at 60 and 120 days, favouring BS over NEM and control.

Conclusion: Both BS and NEM demonstrated significant efficacy in reducing knee OA pain, with BS showing superior results. These findings support their role as effective complementary treatments for OA.

Keywords: Osteoarthritis, Boswellia serrata, Eggshell membrane, Visual Analogue Scale, Knee pain.

Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disease with a prevalence of 22-30% in India.[1] There is a multifactorial cause for OA which includes age, female sex, obesity, physical labour, occupational knee bending, family history, joint damage and vitamin D deficiency. This has been exacerbated by stress, poor posture, infectious diseases and lifestyle disorder.[2] Joint pain is the dominant symptom of OA.[3]Other symptoms include instability, swelling, stiffness and crepitus in the joint. There is diverse pathology in development of OA knee. It includes focal damage and loss of articular cartilage, abnormal remodelling, attrition of subarticular bone, osteophytes formation, laxity of ligaments, synovial inflammation and cyst formation in the subchondral bone as well as periarticular muscle weakness.[4,5] The main triggering factors for development of osteoarthritis are biomechanical. It includes micro-fracture of subchondral bone,

fatigue fracture of collagen fibres or primarily release of proteolytic enzymes as well. Then the whole sequence of events follows resulting in the end stage arthritis. Cytokines in OA are mainly produced by chondrocytes, synoviocytes, and immune cells. Osteoblasts may play a role in remodeling, but they are not the primary source of IL-1β and TNF-α, which plays key role in the catabolic process of cartilage degradation, chondrocyte apoptosis and bone remodelling in OA.[6]

The objectives of treatment in osteoarthritis knee are to reduce symptoms, to improve functional ability and to halt the progression of structural changes. Current treatment modalities of osteoarthritis include non-pharmacological, pharmacological therapies and surgery. Nonpharmacological measures include patient education on daily activities modification and physiotherapy. Pharmacological therapy includes the use of analgesics. Surgical treatments include various orthopaedic surgery such as arthroplasty, arthrodesis etc. Non-steroidal anti-inflammatory drugs (NSAIDs) have long been the preferred therapy because of their analgesic and anti-inflammatory properties, although their use in this condition has sparked controversy.[7]

Currently, alongside traditional treatment, dietary supplements have emerged as a potential adjuvant strategy to counteract pain in chronic disorders such as knee OA or general OA.[8] While guidelines from the National Institute for Health and Care Excellence (NICE)[9], the Osteoarthritis Research Society International (OARSI), and the American College of Rheumatology (ACR) primarily recommend strategies such as physical therapy, weight management, and pharmacological treatments, bioactive compounds under investigation include collagen, glucosamine, and hyaluronic acid or a combination of hyaluronic acid, glucosamine, and chondroitin.[10,11] Interestingly, these compounds are naturally found in the eggshell membrane (ESM), a thin layer located between the calcified shell and the egg white.[12] ESM composed of fibrous proteins such as collagen types I, V, and X; bioactive glycosaminoglycans like dermatan sulfate and chondroitin sulfate and glucosamine.[13] Typically, a 300–500 mg dose of ESM contains these components, allowing for meaningful comparisons to other preparations already used in patients, such as glucosamine, chondroitin sulfate, hyaluronic acid, and collagen hydrolysates. [14,15] Due to its composition, various clinical trials have evaluated ESM as a potential treatment that can promote joint health, reduce pain, and alleviate joint stiffness.[16,17] ESM contains antioxidant peptides, which have been shown to reduce oxidative stress, thereby potentially enhancing its pain-relieving effects. [18]

Boswellic acid is the active ingredient in Boswellia serrata. Research showed that 3-O-Acetyl-11-keto-beta-boswellic acid (AKBA) is the one boswellic acid with strong pharmacological activity; for example, AKBA has a powerful inhibitory effect on 5-lipoxygenase (5-LOX). Clinical studies have shown that Boswellia serrata extract not only has anti-inflammatory and anti-arthritis properties but also improves pain and physical function; in vitro experiments also show that Boswellia serrata extract can inhibit the expression of inflammatory factors such as adhesion molecules.[19] With regard to the safety of Boswellia serrata, studies showed that Boswellia serrata extract (such as 5-Loxin and Aflapin) does not have toxic side effects at higher doses.[20,21]

Despite the growing body of evidence supporting the efficacy of Boswellia serrata extract and ESM in managing OA, there is a lack of comparative studies evaluating their relative effectiveness. This study aims to fill this gap by conducting a comparative evaluation of the efficacy of Boswellia serrata extract and ESM in the management of OA whether Boswellia serrata extract or ESM provides greater overall benefits in the management of OA symptoms.

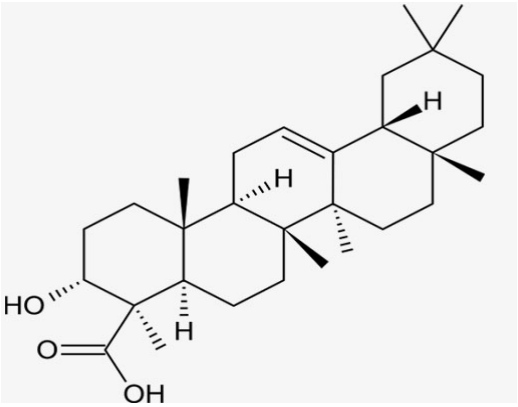


Figure 1: Chemical Structure of Boswellia serrata extract [22]

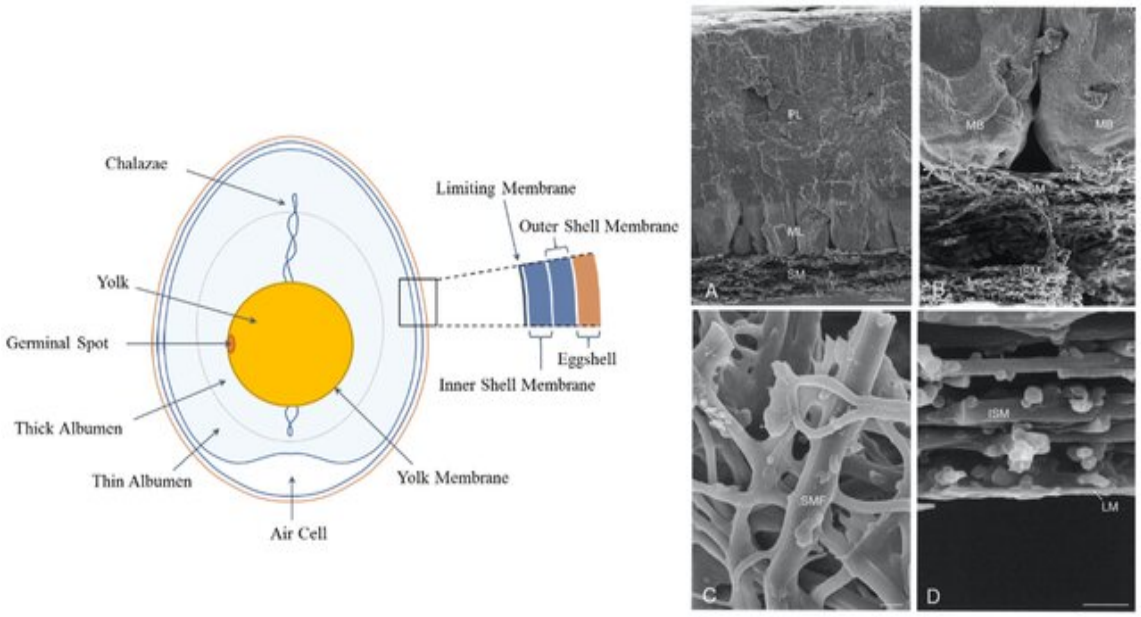


Figure 2: Hen egg structure and scanning electron micrographs illustrating the morphology of the eggshell and eggshell membranes. (A) Eggshell cross-fractured to reveal the shell membrane (SM), mammillary layer (ML), and palisade layer (PL); (B) higher magnification of the membrane mammillary body interface: Outer shell membrane fibers (OSM); insert into the tips of the mammillary bodies (MB); inner shell membranes (ISM); (C) enlargement of the shell membrane fibers (SMF), revealing their interwoven and coalescing nature; (D) inner aspect of the inner shell membrane (ISM), demonstrating the limiting membrane (LM) that surrounds the egg white here removed during sample preparation. Scale bars: (A), 50 mm; (B), 20 mm; (C, D), 2 mm. [23]

Objective: To evaluate pain improvement using the Visual Analogue Scale (VAS) in three groups: Analgesic, Natural Eggshell Membrane (NEM), and Boswellia serrata

Material and Methods

Study Type: Prospective, observational, single-centre study

Study Setting: Department of Pharmacology and Therapeutics in collaboration with the Department of Orthopedics, King George's Medical University, Lucknow, and Uttar Pradesh, India.

Participant Enrollment: Patients diagnosed with knee osteoarthritis were recruited after obtaining informed consent from the Outpatient Department of Orthopedics following ethical approval from the institutional ethics committee.

Study Duration: 18 months.

Sample Size Estimation: Determined using Open-Epi Software. A total of 117 participants (39 in each of the three groups: analgesic, Natural Egg Shell Membrane, and Boswellia Serrata) were enrolled in the study. 10% dropout rate was factored to ensure adequate sample representation.

Procurement of study products: Commercially available Boswellia serrata (Sallaki) 600mg extract was recruited from Gufic Biosciences ltd.

Commercially available Natural egg shell membrane (Fixonem) 500mg was recruited from Ergos life sciences ltd.

Inclusion Criteria:

- Male and female patients aged 35 to 75 years.
- Newly diagnosed with osteoarthritis.
- Patients not currently receiving regular anti-inflammatory drug or dissatisfied with their current medication and seeking a change.
- Patients willing to attend regular follow-up visits.
- Patients able to provide both verbal and written informed consent.

Exclusion Criteria:

- Known hypersensitivity to herbal extracts or dietary supplements.
- Pregnant or lactating women
- Use of Ayurvedic formulations within the past two months.
- Participation in any other clinical trial that ended in the preceding month or is currently ongoing.
- Inflammatory disease

Tools Used in the Study

Semi-Structured Proforma: The proforma included demographic information, medical history, disease characteristics, baseline laboratory investigations and follow-up assessments.

Visual Analogue Scale (VAS): Validated tool to measure pain intensity in clinical and research settings. It consists of a 100mm (10cm) horizontal line with two endpoints: '0' representing 'No Pain' and '10' representing 'Unbearable Pain.' Patients were instructed to mark a point on the scale that best represented their current pain level. Pain assessment was conducted at three time points: baseline (Day 0), Day 60 and 120.

Baseline Investigations: The tests performed included a complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and human leukocyte antigen typing, prothrombin time-international normalized ratio, viral markers, kidney function tests, random blood sugar, serum uric acid, serum creatinine and liver function tests. Patients presenting with abnormal laboratory findings were excluded from the study.

Statistical Analysis: Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Data was entered in Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 26 for Windows. Categorical variables were expressed as numbers and percentages, while continuous variables were presented as mean ± standard deviation (SD) or median values where appropriate. Independent t-tests and one way ANOVA were used to compare continuous variables between groups, and the Chi Square test, Mann Whitney U test and Wilcoxon Signed Ranks Test were used for categorical data. A p-value <0.05 was considered statistically significant.

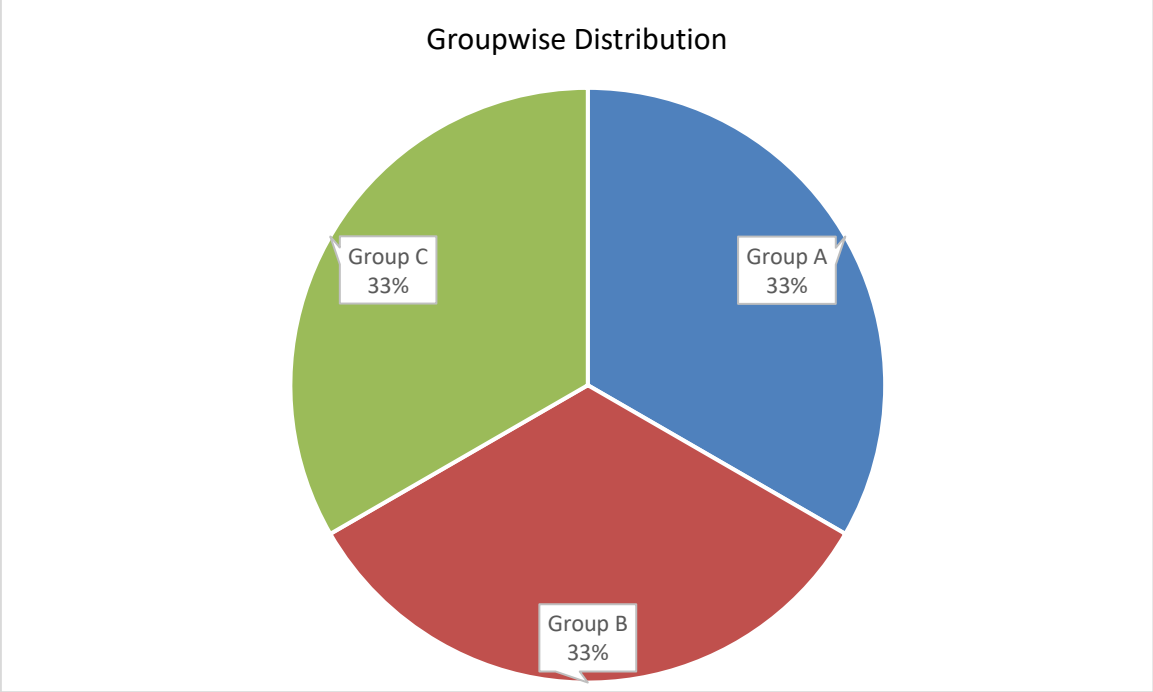
Ethical Considerations: All procedures adhered to the guidelines outlined by the Institutional Ethics Committee and followed the principles of the Declaration of Helsinki.

Appropriate steps for data safety management were implemented to safeguard participant information. Subjects were duly informed of their right to withdraw from the study at any time, with reassurance that their decision would not affect their ongoing care or treatment.

Results and Observation:

Table 1: Group Wise Distribution of Study Population

S. No.	Group	Description	Frequency (%)
1	A	Etoricoxib 60 mg twice daily (BD)	39 (33.3%)
2	B	Etoricoxib 60 mg BD along with Natural Egg Shell Membrane (Fixonem) 500 mg once daily (OD)	39 (33.3%)
3	C	Etoricoxib 60 mg BD in combination with Boswellia Serrata (Sallaki) 600 mg BD	39 (33.3%)



Graph 1: Group wise distribution

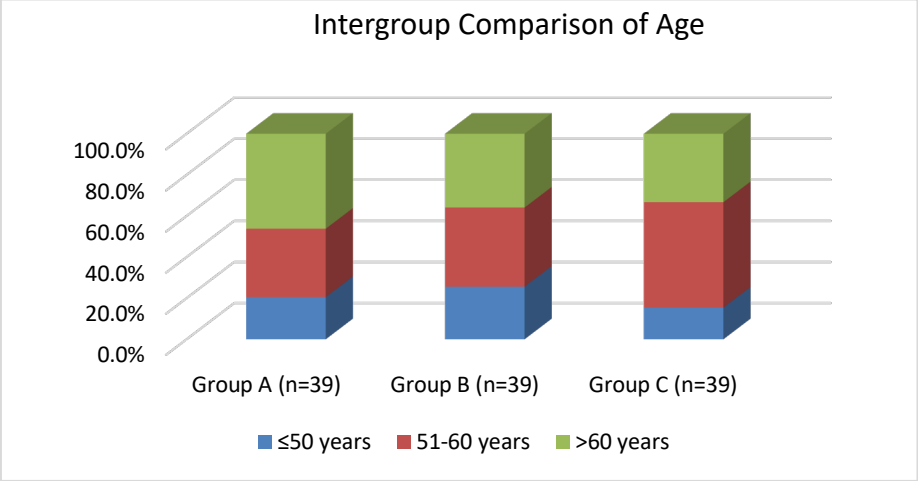
Out of 117 patients who completed the study, 39 (33.3%) received Etoricoxib 60 mg twice daily (BD) and were classified as Group A, 39 (33.3%) received Etoricoxib 60 mg BD along with Natural Egg Shell Membrane

(Fixonem) 500 mg once daily (OD) and were classified as Group B, and 39 (33.3%) received Etoricoxib 60 mg BD in combination with Boswellia Serrata (Sallaki) 600 mg BD and were classified as Group C.

Table 2: Intergroup Comparison of Age

Age Group	Group			χ2 value	P value
	Group A (n=39)	Group B (n=39)	Group C (n=39)		
≤50 years	8 (20.5%)	10 (25.6%)	6 (15.4%)	3.559#	0.469
51-60 years	13 (33.3%)	15 (38.5%)	20 (51.3%)		
>60 years	18 (46.2%)	14 (35.9%)	13 (33.3%)		
Age	58.46±10.65	56.67±8.78	57.51±8.27	0.364*	0.696

#Chi Square test; *One Way ANOVA



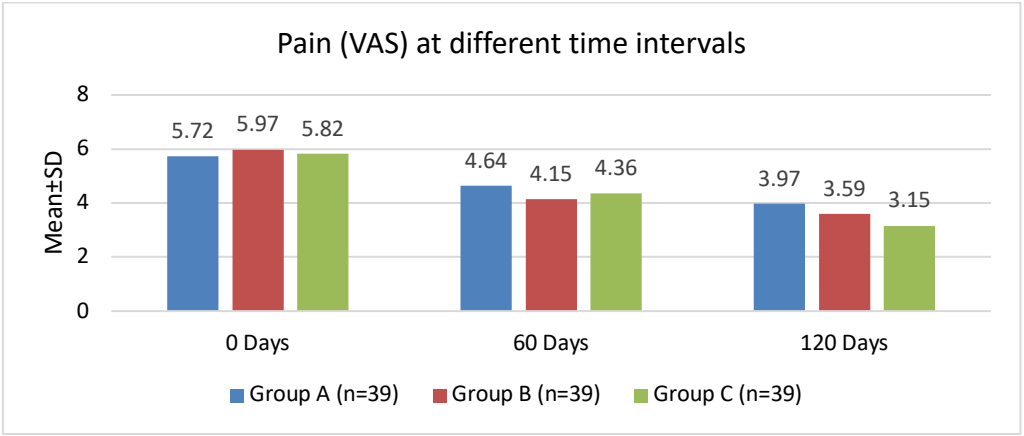
Graph 2: Intergroup comparison of age

The mean age of the study population was comparable across all groups (p=0.696). A higher proportion of patients in Group C (51.3%) belonged to the 51-60 years age group, whereas in Group A, the majority of patients (46.2%) were above 60 years of age. In Group B, the distribution was relatively balanced, with 38.5% of patients in the 51-60 years age group and 35.9% in the >60 years age group. The intergroup comparison of age was not statistically significant (p=0.469).

Table 3: Intergroup Comparison of Pain (VAS) at different time intervals

VAS score	Group A (n=39)	Group B (n=39)	Group C (n=39)	F value	P value
0 Days	5.72±0.92	5.97±0.58	5.82±0.79	1.079	0.343
60 Days	4.64±0.87	4.15±0.43	4.36±0.67	5.016	0.008
120 Days	3.97±0.1.01	3.59±0.59	3.15±0.59	11.442	<0.001

***One Way ANOVA**



Graph 3: Pain (VAS) at different level

At 0 days, the mean VAS scores were 5.72±0.92, 5.97±0.58, and 5.82±0.79 for Group A, Group B, and Group C, respectively. There was no significant difference in pain scores between the three groups at this time point (F=1.079, p=0.343). However, at 60 days, the mean VAS scores were 4.64±0.87, 4.15±0.43, and 4.36±0.67 for Group A, Group B, and Group C, respectively, with a significant difference between the groups (F=5.016, p=0.008). Furthermore, at 120 days, the mean VAS scores were 3.97±1.01, 3.59±0.59, and 3.15±0.59 for Group A, Group B, and Group C, respectively, with a highly significant difference between the groups (F=11.442, p<0.001).

Table 4: Between group Comparison of VAS score at different time intervals (Mann Whitney U test)

VAS score	Day 0		Day 60		Day 120	
	Z value	P value	Z value	P value	Z value	P value
Group A vs. B	1.254	0.210	2.790	0.005	1.853	0.064
Group A vs. C	0.465	0.642	1.193	0.233	3.825	<0.001
Group B vs. C	0.832	0.406	1.878	0.060	2.946	0.003

By using the Mann Whitney U test in this table, we noted that at Day 0, there were no significant differences in VAS scores between Group A vs. B (Z=1.254, p=0.210), Group A vs. C (Z=0.465, p=0.642), or Group B vs. C (Z=0.832, p=0.406). However, at Day 60, a significant difference in VAS scores was observed between Group A vs. B (Z=2.790, p=0.005), but not between Group A vs. C (Z=1.193, p=0.233) or Group B vs. C (Z=1.878, p=0.060). Furthermore, at Day 120, significant differences in VAS scores were observed between Group A vs. C (Z=3.825, p<0.001) and Group B vs. C (Z=2.946, p=0.003), but not between Group A vs. B (Z=1.853, p=0.064).

Table 5: Intragroup Change in Baseline Pain (VAS Day 0) (Wilcoxon Signed Rank Test)

VAS Score		Group A	Group B	Group C
0 vs. 60 days	Mean	1.08	1.82	1.46
	SD	0.53	0.68	0.85
	% Change	18.9%	30.5%	25.1%
	Z value	-5.514	-5.561	-5.273
	P value	<0.001	<0.001	<0.001
0 vs. 120 days	Mean	1.74	2.38	2.67
	SD	0.72	0.91	0.81
	% Change	30.4%	39.9%	45.9%
	Z value	-5.498	-5.410	-5.541
	P value	<0.001	<0.001	<0.001
60 vs. 120 days	Mean	0.67	0.56	1.21
	SD	0.57	0.68	0.66
	% Change	14.4%	13.5%	27.8%
	Z value	-4.747	-4.017	-5.273
	P value	<0.001	<0.001	<0.001

By using the Wilcoxon Signed Ranks Test this study noted that there was a significant reduction in pain scores at all time points. From Day 0 to Day 60, the mean reduction in pain scores was 1.08 (SD=0.53) in Group A, 1.82 (SD=0.68) in Group B, and 1.46 (SD=0.85) in Group C, with percentage changes of 18.9%, 30.5%, and 25.1%, respectively (all p<0.001).

From Day 0 to Day 120, the mean reduction in pain scores was 1.74 (SD=0.72) in Group A, 2.38 (SD=0.91) in Group B, and 2.67 (SD=0.81) in Group C, with percentage changes of 30.4%, 39.9%, and 45.9%, respectively (all p<0.001).

Additionally, from Day 60 to Day 120, the mean reduction in pain scores was 0.67 (SD=0.57) in Group A, 0.56 (SD=0.68) in Group B, and 1.21 (SD=0.66) in Group C, with percentage changes of 14.4%, 13.5%, and 27.8%, respectively (all p<0.001). These results indicate a significant reduction in pain scores over time within each group.

Discussion

Knee osteoarthritis (KOA) represents a degenerative bone and joint condition that affects both men and women, primarily middle-aged and older adults. Its prevalence is on the rise as the population ages.[24] OA of the knee and hip is a major cause of global disability, imposing substantial economic burdens.[25] The Global Burden of Disease (GBD) is on the rise, currently impacting 7.6% of the global population, suggesting the prevalence will be increased by 132.2% over 30 years and is projected to rise by 60 to 100% by 2050 of disability.[26] The estimated

costs range from 1 to 2.5% of the gross domestic product (GDP) in Western countries.[27] Wage losses due to OA amount to $65 billion, and direct medical costs exceed $100 billion.[28] People with knee OA spend, on average, around $15,000 dollars (discounted) on the medical treatment of OA over their lifetimes.[29]

Clinical guidelines currently advocate non-steroidal anti-inflammatory drugs (NSAIDs) as treatments for OA.[30] However, prolonged use of NSAIDs has been linked to undesirable side effects, including gastrointestinal complications, cardiovascular conditions, potential harm to the kidneys and liver.[31] Nutraceuticals, encompassing glycosaminoglycans and certain botanical extracts, have exhibited promise in reducing pain, improving function, and preserving joint space width.[32] Approximately 30% of OA patients have incorporated supplements into their treatment regimen.[33] An escalating body of research endorses the therapeutic effect of dietary supplements for KOA.[34] Nevertheless, because of a lack of reproducibility in evidence and variabilities between dietary supplement manufactures,[35] the optimal dietary supplement for this condition remains highly debatable.

In our study, the 41.0% patients belonging to 51-61 years age group, followed by 38.5% were having >60 years age group and only 20.5% patients were in ≤50 age group. The mean age of the study population was comparable across all groups (p=0.696).

The intergroup comparison of age was not statistically significant (p=0.469). Park S et al[36] reported mean age of the total participants was 58.14 ± 7.99 years, Kannan et al[37] reported mean age was 55.08±8.75 years. This shift in age of onset of OA towards relatively younger population was also described by Bhatia et al [38] in their study. Reason for this shift towards a younger age of 41-60 years is of multiple etiologies consisting of lifestyle, dietary, habitual and environmental changes as described by Magrans et al.[39]

VAS Pain at different time intervals

At baseline (0 days), VAS pain scores showed no significant differences between the three groups. However, at 60 days, significant differences emerged, with VAS (p=0.008) scores indicating varying degrees of pain reduction among the groups. By 120 days, the differences between the groups became even more pronounced, with highly significant differences in VAS (p<0.001) scores.

Dubey V et al [40] concluded that Boswellia Serrata supplementation significantly reduced pain (VAS) and OA-related symptoms compared to control therapy. Muller C et al [41] concluded that eggshell membrane-based supplement showed a small improvement in mobility and inflammatory biomarkers, hence the symptoms.

Intergroup comparison

Mann-Whitney U test revealed no significant differences in VAS pain scores between the groups at baseline (Day 0). However, at Day 60, significant differences emerged in VAS scores between Group A and B (p=0.005). By Day 120, significant differences were observed in VAS scores between Group A and C (p<0.001) and Group B and C (p=0.003). However, at Day 60, a significant difference emerged between Group A and B (p=0.024). By Day 120, significant differences were observed between Group A and B (p<0.001) and Group A and C (p<0.001), but not between Group B and C. However, at Day 60 and Day 120, significant differences emerged between all group pairs, including Group A vs. B, Group A vs. C, and Group B vs. C (all p<0.001). Choi YJ et al [42] reported that the standardized Boswellia serrata gum resin extract (BSRE) significantly reduced knee joint swelling, cartilage destruction, and tissue deformation in osteoarthritis-induced rats. These results suggest that the interventions had a differential impact on pain reduction over time, with varying degrees of significance between the groups at different time points.

Intragroup

Our study noted that a significant reduction in pain scores within each group over time. Using the Wilcoxon Signed Ranks Test, the results showed that from Day 0 to Day 60, Day 0 to Day 120, and Day 60 to Day 120, there were significant reductions in VAS pain scores in all three groups (all p<0.001). The percentage changes in VAS scores ranged from 18.9% to 45.9%, indicating substantial pain reduction over time.

Limitations: The study had a relatively small sample size and the follow-up period was limited to 120 days.

Strengths: Study's comparative design allows for a direct comparison of the efficacy of Natural Egg Shell Membrane and Boswellia Serrata in patients with knee osteoarthritis. Usage of standardized outcome measures the VAS scores which are widely accepted and validated measures of pain.

Conclusion

This study highlights the effectiveness of both Natural Eggshell Membrane (NEM) and Boswellia Serrata in managing symptoms of knee osteoarthritis. Both treatment groups experienced significant reductions in pain, as assessed by the Visual Analogue Scale (VAS) over the study period. Notably, the Boswellia Serrata group demonstrated a marginally greater reduction in pain scores compared to the NEM group. Intragroup

analysis revealed that both treatment arms achieved statistically significant reductions in pain over time. Intergroup comparisons indicated that Boswellia Serrata had superior outcomes in terms of pain relief as compared to the Natural Eggshell Membrane.

Clinical Implications

The findings suggest that both Boswellia Serrata and Natural Eggshell Membrane are effective in alleviating pain in individuals with knee osteoarthritis.

These results support their consideration as alternative or complementary therapeutic options in clinical practice.

Recommendations

Boswellia Serrata and Natural Eggshell Membrane may serve as viable treatment choices for patients with knee osteoarthritis, particularly for those seeking non-conventional or plant-based remedies. Further research should compare these agents with conventional pharmacological therapies and other non-pharmacological modalities to evaluate relative efficacy and safety.

Future Directions

Long-term studies are needed to evaluate the sustained efficacy and safety of both treatments.

Investigations into the mechanisms of action and possible interactions with other medications will be crucial for optimizing their use in clinical settings.

References:

1. Das AK, Routray D, Panigrahi TK. Prevalence and risk factors of knee osteoarthritis in a rural community of Odisha: A snapshot study. 2018; 15–21.
2. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015; 23(4):507–15.
3. Zhang Y, Jordan JM. Epidemiology of Osteoarthritis. Clin Geriatr Med. 2010; 26(3):355–69.
4. Pelletier JP, Martel-Pelletier J. Therapeutic targets in osteoarthritis: from today to tomorrow with new imaging technology. Ann Rheum Dis. 2003; 62(2):79–82.
5. Pelletier J, Martel-pelletier J, Abramson SB. Osteoarthritis, an Inflammatory Disease Potential Implication for the Selection of New Therapeutic Targets. Arthritis Rheum. 2001; 44(6):1237–47.
6. Kobayashi M, Squires GR, Mousa A, Tanzer M, Zukor DJ, Antoniou J, et al. Role of interleukin-1 and tumour necrosis factor alpha in matrix degradation of human osteoarthritic cartilage. Arthritis Rheum. 2005; 128–35.
7. Dingle J. Cartilage maintenance in osteoarthritis: Interaction of cytokines, NSAID and prostaglandins in articular cartilage damage and repair. J Rheumatol Suppl. 199.
8. Mora JC, Przkora R, Cruz-Almeida Y. Knee Osteoarthritis: Pathophysiology and Current Treatment Modalities. J Pain Res. 2018; 2189–96.
9. Chaplin S. NICE on the Diagnosis and Management of Osteoarthritis. Prescriber. 2023; 15–6.
10. García-Coronado JM, Martínez-Olvera L, Elizondo-Omaña RE, Acosta-Olivo CA, Vilchez-Cavazos F, Simental-Mendía LE, et al. Effect of Collagen Supplementation on Osteoarthritis Symptoms: A Meta-Analysis of Randomized Placebo-Controlled Trials. Int Orthop. 2019; 531–8.
11. Kiers JL, Bult JHF. Mildly Processed Natural Eggshell Membrane Alleviates Joint Pain Associated with Osteoarthritis of the Knee: A Randomized Double-Blind Placebo-Controlled Study. J Med Food. 2021; 291–8.
12. Han C, Chen Y, Shi L, Chen H, Li L, Ning Z, et al. Advances in Eggshell Membrane Separation and Solubilization Technologies. Front Vet Sci. 2023;
13. Nakano T, Ikawa N, Ozimek L. Chemical Composition of Chicken Eggshell and Shell Membranes. Poult Sci. 2003; 510–4.
14. Hewlings S, Kalman D, Schneider LV. A Randomized, Double-Blind, Placebo-Controlled, Prospective Clinical Trial Evaluating Water-Soluble Chicken Eggshell Membrane for Improvement in Joint Health in Adults with Knee Osteoarthritis. J Med Food. 2019; 875–84.
15. Cánovas F, Abellán-Ruíz MS, García-Muñoz AM, Luque-Rubia AJ, Victoria-Montesinos D, Pérez-Piñero S, et al. Randomised Clinical Trial to Analyse the Efficacy of Eggshell Membrane to Improve Joint Functionality in Knee Osteoarthritis. Nutrients. 2022.
16. Kannan R, Bakthavatchalam S, Murugesan S, Kumar B, Deb B, Marimuthu C, et al. A Randomized, Open-Label, Multicentered Parallel-Group Clinical Study to Evaluate the Efficacy and Safety of Joint CoreTM Compared to Jointace DNTM in Osteoarthritis Patients. J Curr Res Sci Med. 2022; 44–51.
17. Ruff KJ, Winkler A, Jackson RW, DeVore DP, Ritz BW. Eggshell Membrane in the Treatment of Pain and Stiffness from Osteoarthritis of the Knee: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Clinical Study. Clin Rheumatol. 2009; 907–14.
18. Zhao QC, Zhao JY, Ahn DU, Jin YG, Huang X. Separation and Identification of Highly

Efficient Antioxidant Peptides from Eggshell Membrane. Antioxidants. 2019.
19. Yu G, Xiang W, Zhang T, Zeng L, Yang K, Li J. Effectiveness of Boswellia and Boswellia extract for osteoarthritis patients: a systematic review and meta-analysis. BMC Complement Med Ther. 2020 Jul 17; 20(1).
20. Lalithakumari K, Krishnaraju AV, Sengupta K, et al. Safety and toxicological evaluation of a novel, standardized 3-O-acetyl-11-keto-β-boswellic acid (AKBA)-enriched Boswellia serrata extract (5-Loxin) Toxicol Mech Methods. 2006; 199–226.
21. Krishnaraju AV, Sundararaju D, Vamsikrishna U, et al. Safety and toxicological evaluation of Aflapin: a novel Boswellia-derived anti-inflammatory product. Toxicol Mech Methods. 2010; 556–63.
22. Gerhard Hoermann. Boswellia serrata [Internet]. Fitness informant. [Cited 2025 Sep 13]. Available from: https://fitnessinformant. com/ingredients/boswellia/
23. Shi Y, Zhou K, Li D, Guyonnet V, Hincke MT, Mine Y. Avian eggshell membrane as a novel biomaterial: A review. Vol. 10, Foods. MDPI; 2021.
24. Atun R. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Vol. 386, the Lancet. Lancet Publishing Group; 2015. p. 721–2.
25. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. Br J Sports Med. 2018; 52:167–75.
26. Chandra R, Kumar R, Haque S, Katiyar DK, Singh A. COX-2 Selectivity and Beyond: Exploring Polmacoxib Role in Knee Osteoarthritis Treatment. Int J of Pharm Sci [Internet]. 2025 Apr 17; 3(4):2157–65. Available from: https://www.ijpsjournal.com
27. Hiligsmann M, Cooper C, Arden N, Boers M, Branco JC, Brandi LM, et al. Health economics in the field of osteoarthritis: an expert's consensus paper from the European Society for Clinical and Economic Aspects of osteoporosis and osteoarthritis (ESCEO). Semin Arthritis Rheum. 2013; 43:303–13.
28. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: A review. JAMA. 2021; 325:568–78.
29. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI Guidelines for the Non-Surgical Management of Knee, Hip, and Polyarticular Osteoarthritis. Osteoarthr Cartil. 2019; 27:1578–89.
30. Kan HS, Chan PK, Chiu KY, Yan CH, Yeung SS, Ng YL, et al. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J. 2019; 25:127–33.
31. Da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ. 2021; 375.
32. Kiers JL, Bult JHF. Mildly Processed Natural Eggshell Membrane Alleviates Joint Pain Associated with Osteoarthritis of the Knee: A Randomized Double-Blind Placebo-Controlled Study. J Med Food 2021; 24:292–298. 2021; 24:292–8.
33. Gregory PJ, Sperry M, Wilson AF. Dietary supplements for osteoarthritis. Am Fam Physician. 2008; 77:177–84.
34. Srivastava S, Chaudhary JA, Girandola RN. Effect of E-OA-07 on improving joint health and mobility in individuals with knee osteoarthritis: a randomized, double-blind, placebo-controlled, parallel group study. J Pain Res. 2019; 12:3365–79.
35. Brophy RH, Fillingham YA. AAOS clinical practice guideline summary: Management of Osteoarthritis of the knee (non-arthroplasty). J Am Acad Orthop Surg. 2022; 30.
36. Park S, Ko SH, Yoon NK, Kim BK, Kim J, Kang EB, et al. Efficacy of natural eggshell membrane for knee osteoarthritis: A randomized, double-blind, placebo-controlled clinical trial. J Funct Foods. 2024.
37. Kannan R, Bakthavatchalam S, Murugesan S, Kumar B, Deb B, Marimuthu C, et al. A Randomized, Open-Label, Multicentered Parallel-Group Clinical Study to Evaluate the Efficacy and Safety of Joint CoreTM Compared to Jointace DNTM in Osteoarthritis Patients. J Curr Res Sci Med. 2022; 8:44–51.
38. Bhatia D, Bejarano T, Novo M. Current interventions in the management of knee osteoarthritis. J. J Pharm Bioallied Sci. 2013; 5(1).
39. Magrans-Courtney T, Wilborn C, Rasmussen C, Ferreira M, Greenwood L, Campbell B, et al. Effects of diet type and supplementation of glucosamine, chondroitin, and MSM on body composition, functional status, and markers of health in women with knee osteoarthritis initiating a resistance-based exercise and weight loss program. J Int Soc Sports Nutr. 2011; 8(1).
40. Dubey V, Kheni D, Sureja V. Efficacy evaluation of standardized Boswellia serrata extract (Aflapin®) in osteoarthritis: A systematic review and sub-group meta-analysis study. Explore (NY). 2024; 20(5).

41. Muller C, Enomoto M, Buono A, Steiner JM, Lascelles BD. Placebo-controlled pilot study of the effects of an eggshell membrane-based supplement on mobility and serum biomarkers in dogs with osteoarthritis. Vet J. 2019; 253.

42. Choi YJ, Jung JI, Bae J, Lee JK, Kim EJ. Evaluating the Anti-Osteoarthritis Potential of Standardized Boswellia serrata Gum Resin Extract in Alleviating Knee Joint Pathology and Inflammation in Osteoarthritis-Induced Models. Int J Mol Sci. 2024; 25(6).