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Original Research Article

Real world evidence of effectiveness and safety of an oral formulation containing un-denatured type-II collagen 40 mg and aflapin 100 mg (HAPID®) in the management of osteoarthritis of knee: findings of a prospective, multi-center, observational study

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ABSTRACT

Background: Osteoarthritis (OA) of knee is a common progressive multifactorial joint disorder affecting the quality of life, and surgical repair is the final option which has substantial impact on healthcare costs. This real-world study evaluates the efficacy and safety of an oral formulation containing UC-II and aflapin (Boswellia serrata extract enriched in 3-O-acetyl-11-keto-beta-boswellic acid) for treatment of OA of knee.
Methods: Data of 505 ambulatory adult patients (study duration-Jul-21 to Jul-22) of either gender (227 M, 278 F) having OA of knee, and who received study treatment (capsule HAPID®, Wockhardt, India) once daily for a period of up to 90 days were included for the study after obtaining informed written consent. Primary outcomes were mean change in Western Ontario and McMaster universities OA index (WOMAC) scores from baseline through day 90 (total and sub-scales for joint pain, joint stiffness, and physical function), and change in 0-10 visual analogue scale (VAS) score for pain.
Results: About 285 (56.4%) patients were newly diagnosed, majority (63.4%) were having grade 2 severity of OA (Kellgren and Lawrence grade). The mean (SD) baseline total WOMAC scores improved from 60.94 (23.60) at baseline to 26.42 (22.19) on day 90. Significant improvements were seen starting from day 5 ($p=0.023$) and progressively up to day 90 ($p<0.0001$).
Conclusions: The excellent safety and efficacy profile of combination therapy with aflapin and UC-II makes it a desirable pharmacological treatment modality for management of patients of knee OA.

Keywords: Osteoarthritis, Aflapin, Type-II collagen, *Boswellia serrata*

INTRODUCTION

Osteoarthritis (OA) of knee is a common progressive multifactorial joint disorder and is characterized by chronic pain, stiffness, and functional disability.[1] It accounts for almost four fifths of the burden of OA worldwide and increases with obesity and age.[2] The pooled global prevalence of knee OA was 16% (95% CI, 14.3-17.8%) and the prevalence increases with age.[3] However, the prevalence of the OA of knee is higher in the Asian continent (19.2%; 95% CI, 15.7%-23%) compared to Europe (13.4%; 95% CI, 10.1%-17%) and North

America (4·1%; 95% CI, 2.1%-6.9%).[3] Also, literature shows a higher prevalence and incidence of knee OA in women (21.7%; 95% CI, 19%-24.5%) as compared to men (11.9%; 95% CI, 10.2%-13.8%).[3,4] The prevalence of OA of the knee in India is found to be 28.7%.[5] In an Indian hospital-based study, 58% of females had onset of symptoms of OA of knees before 50 years of age as compared to only 20% in males ($p<0.05$).[6] Also, 64% females with OA of knees had the onset of symptoms either during perimenopausal period or within five years of natural menopause or hysterectomy. The pathological changes in later stage of OA which includes softening, ulceration, and disintegration of the articular cartilage.[7] Based on the radiology, OA of knee is classified using the Kellgren and Lawrence classification system, which grades the OA severity from grade-0 (no OA) to grade 4 (severe OA).[8] OA of the hips and knees tends to cause the greatest burden to the population as pain and stiffness in these large weight bearing joints often leads to significant disability requiring surgical intervention.[9] OA of knee is incurable and the only cure is surgical repair which is considered only at an advanced stage of the disease; however, it involves substantial healthcare costs.[10]

The management of OA focuses on multi-modal treatment including patient education and self-management, non-pharmacological management, and pharmacological treatments. Non-pharmacologic therapy includes patient education, weight loss (5% over 20 weeks), moderate exercises, physical therapy, and occupational therapy.[11] Pharmacological management of OA includes paracetamol, non-steroidal anti-inflammatory drugs (NSAID), opioid analgesics, intra-articular drugs, and disease modifying OA drugs (DMOAD). However, there are no DMOADs yet approved for OA, and some are in clinical development (targeted against Bone morphogenetic protein-7 (BMP-7), fibroblast growth factor-18 (FGF-18), platelet rich plasma (PRP), matrix metalloproteinases (MMPs), and mesenchymal stem cells (MSCs). NSAIDs and corticosteroids are associated with high prevalence of gastrointestinal/ cardiovascular adverse effects. All efforts to develop safe NSAIDs that spare the gastrointestinal tract and the cardiovascular effects are still far from achieving a breakthrough. Hence, there is a need for a safe and effective alternative for management of OA.

Many nutraceutical products like Boswellia, Aflapin, chondroitin sulphate, glucosamine sulphate, collagen peptide, curcumin, fish oil, ginger, green tea, and rosehip extract have been used for treatment of OA of knee but with varied results.[12] Gum resin extracts of *Boswellia serrata* have shown anti-inflammatory properties and promising potential as therapeutic interventions against inflammatory diseases like OA. Aflapin is synergistic composition of *Boswellia serrata* extract enriched in AKBA (3-O-Acetyl-11-keto-beta-boswellic acid) and non-volatile oil portion of *B. serrata* gum resin.[13] Undenatured form of type II collagen (UC-II) is nutritional supplement derived from chicken sternum cartilage which plays important role in building of joint cartilage and may also have anti-inflammatory and antioxidant effects.[14] Study published in science in 1993 reported reduced joint swelling with oral type II collagen supplementation in RA.[15] It is expected that compared to NSAIDs, *B. serrata* extract and UC-II may associated with better tolerability.

The present real-world study is the first in India and probably worldwide which evaluates the efficacy and safety of an oral formulation containing UC-II and aflapin for treatment of OA of knee.

METHODS

Setting

This study was a prospective, post-marketing, real-world, observational study conducted for assessment of effectiveness and efficacy of an oral formulation containing UC-II and aflapin for treatment of OA of knee. Data was collected from 20 participating sites across India. study duration-Jul-21 to Jul-22.

Informed consent and ethics

In this post-marketing study, data of patients who were prescribed treatment with oral tablet containing un-denatured type-II collagen 40mg and aflapin 100 mg (HAPID®, Wockhardt, India) for treatment of knee OA was collected prospectively from the participating sites. The study documents were reviewed and approved by the institutional ethics committee (IEC) of D. Y. Patil university school of medicine, Navi Mumbai (DYP/IEC/12/2021, June 10, 2021). The study was conducted in accordance with the principles of declaration of Helsinki (World medical association) and good clinical practice (GCP) guidelines issued by the ICMR and CDSCO, government of India, and was registered with the clinical trials registry of India (CTRI/2021/07/034559, July 02, 2021). This being a prospective study, informed consent was obtained from all the patients, and the strict confidentiality was maintained for the patient's identity.

Study participants

Data of 505 patients of either gender above 18 years of age who received study treatment were included for the study. Ambulatory adult patients with clinically and/or radiologically confirmed diagnosis of OA of knee and prescribed capsule HAPID® (Un-denatured type II collagen and Aflapin) for first time, willing to provide written informed consent and comply to the study as per protocol were included in the study. Those with a history or evidence of hypersensitivity to any components of study medication, or those who received visco-supplementation (hyaluronic acid injection in joints) within 9 months prior to date of screening were excluded. Pregnant or lactating women, and patients with known allergy to eggs/ chicken were not included.

Study procedures

Data was collected and recorded in a study specific electronic data capture tool from the participating sites. Patient information about their clinical condition on admission, comorbidities, complications, and details of other treatment (including analgesic and anti-inflammatory drugs) received was collected. This being an observational study, there were no study specific treatments and all treatments for the patients were based at the discretion of the treating clinician. All patients received capsule containing Aflapin 100 mg and un-denatured type II collagen 40 mg orally as per investigator's discretion for a period of 90 days.

The study outcomes were based on the Western Ontario and McMaster Universities OA Index (WOMAC), which is valid and reliable for defining function in lower extremity disorders.[16] WOMAC consists of a total of 24 questions and three subscales (5 questions related to pain, two questions related to stiffness, and 17 questions related to difficulties in performing activities of daily living in relation to physical function). Pain was assessed using a 0-10 visual analogue scale (VAS). Assessments were done at baseline and then on days 5, 30, 60 and 90 days.

Rescue analgesic

Use of any rescue analgesic (paracetamol 500 mg as per need) for breakthrough pain during study period recorded.

Study outcomes

The primary outcomes for effectiveness were mean change in total WOMAC score from baseline through day 90, mean change in VAS score for pain from baseline through day 90, and mean change in scores for WOMAC subscales (joint pain, joint stiffness, and physical function) from baseline through day 90. Secondary endpoints were for safety and tolerability assessed based on the adverse events reported with the study treatment.

Statistical methods

This being an observational study, there was no study hypothesis. Due to lack of published literature on efficacy of combined treatment with UC-II and aflapin in OA knee, the sample size was not based on any assumptions and calculations, and it was planned to include data of 500 patients on empirical basis. Data were entered in Microsoft office excel worksheet and checked for discrepancies and errors. Descriptive are presented for demography and study outcomes (WOMAC score and VAS score). Measurement data are presented as means and standard deviation (SD), whereas categorical data is presented as numbers with percentages. Within group analysis of baseline data with follow-up visits data (Day 5, 30, 60 and 90) is done for WOMAC scores (total and subscale) and VAS scores using Friedman test (repeat measures non-parametric ANOVA). Individual pair-wise comparisons with baseline are done using Wilcoxon test for paired data. All analyses were done using two-sided tests with alpha 0.05 (95% confidence levels). Statistical analysis was done using Stata 13.1 for Windows (StataCorp LLC, TX, USA).

RESULTS

Patient characteristics and pre-treatment data

Of the 505 patients included for the final analysis, there were 45% male and 55% females. Table 1 shows demography and patient profile of all patients included in study. About 56.4% patients newly diagnosed knee OA. Most of patients (96%) received 90 days of study treatment and only 20 (4%) patients received 60 days treatment.

Table 2 shows prev. medication received by patients, and concomitant medication received along with study treatment. Other therapies received by patients in past were oral NSAID's (19.2%), topical NSAID's (1.4%), exercise therapy (5.1%), weight loss (2.6%), and other therapies (0.6%). Other therapies received by the patients were antihypertensives (1.6%), oral hypoglycaemics (0.6%) and thyroxine (0.4%).

WOMAC score

Table 3 presents the WOMAC scores for the three sub-scales and the total score at baseline and change from baseline on days 5, 30, 60 and 90. Improvements are seen from baseline for all 3 sub-scale scores and total scores on WOMAC scale immediately on day 5 with study treatment. There is progressive improvement up to day 90 with gross reductions in mean scores on day 90. Figure 1 presents mean scores for WOMAC physical function sub-scale and total scores from baseline through day 90. Figure 2 shows mean scores for WOMAC pain and stiffness sub-scale scores from baseline through day 90. Statistically significant reduction ($p<0.0001$) in all sub-scale scores and total scores for WOMAC seen over 90 days.

Pain (VAS) score

Table 4 presents the pain scores (0-10 VAS) at baseline and change from baseline on days 5, 30, 60 and 90. Figure 3 presents the mean scores for pain (0-10 VAS) from baseline through day 90. Great reduction in the pain scores is seen over 90 days ($p<0.0001$).

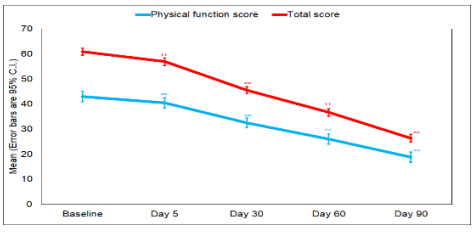

Figure 1: WOMAC physical function and total scores at baseline and over 90 days.

* $p<0.05$; ** $p<0.001$ (Versus baseline, Wilcoxon test).

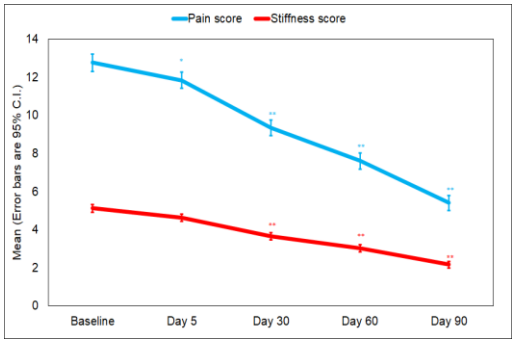

Figure 2: WOMAC pain and stiffness sub-scale scores at baseline and over 90 days.
* p<0.05; ** p<0.001 (Versus baseline, Wilcoxon test).

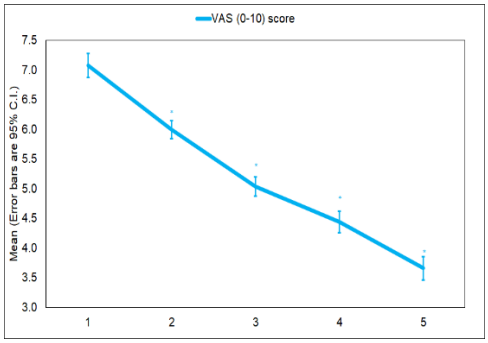

Figure 3: Mean (95% C.I.) pain scores (0-10 VAS) at baseline and over 90 days.
*P<0.001 (Versus baseline, Wilcoxon test).

Table 1: Demography and patient profile.

Variables	Mean	SD (Range)
Age (Years), n=505	56.59	9.51 (24-86)
BMI (kg/sq.m), n=505	27.61	3.50 (19.75-38.82)
Duration of OA (Years), n=220	2.98	1.97 (0.10-10.70)
Gender, n=505		
Male	227	45
Female	278	55
BMI category (WHO), n=505		
Normal weight	113	22.4
Overweight	282	55.8
Obese (Class I)	90	17.8
Obese (Class II)	20	4
Duration of study treatment, n=505		
60 days	20	4
90 days	485	96
Diagnosis of OA, n=505		
Newly diagnosed OA	285	56.4
Old C/O knee OA	220	43.6
Kellgren and Lawrence grade of OA, n=505		
Grade-0	4	0.8
Grade-1	76	15
Grade-2	320	63.4
Grade-3	54	10.7
Grade-4	51	10.1
Concomitant medical condition, n=505		
Diabetes mellitus	6	1.2
Hypertension	3	0.6
Thyroid disorder	2	0.4
Total	11	2.2

Table 2: Concomitant medication and past medication used for OA.

Variables	N	Percentages (%)
Concomitant drugs used, n=505		
Oral hypoglycemic agent	6	1.2
Angiotensin receptor blocker	3	0.6
Thyroxin	2	0.4
Total	11	2.2
Drugs used in past for knee OA, n=505		

Continued.

Variables	N	Percentages (%)
Aceclofenac	19	3.8
Diclofenac	55	10.9
Etoricoxib	6	1.2
Glucosamine	2	0.4
Ibuprofen	7	1.4
Naproxen	1	0.2
Nimesulide	4	0.8
Paracetamol	3	0.6
Tramadol	1	0.2
Total pts. with past use of drugs	85	16.8
N/A	420	83.2

Table 3: WOMAC baseline scores and change from baseline over 90 days.

Variables	No.	Mean	Median	SD	P (Versus baseline)*
WOMAC pain sub-scale score					
Baseline	505	12.76	13.00	5.15	<0.0001#
Change from baseline					
Day 5	496	0.92	1.00	0.24	0.023
Day 30	494	3.42	3.00	0.62	<0.0001
Day 60	486	5.16	6.00	0.42	<0.0001
Day 90	485	7.35	8.00	0.80	<0.0001
WOMAC joint stiffness sub-scale score					
Baseline	505	5.12	5.00	2.29	<0.0001#
Change from baseline					
Day 5	496	0.50	0.00	0.06	0.002
Day 30	494	1.47	1.00	0.19	<0.0001
Day 60	486	2.09	2.00	0.24	<0.0001
Day 90	485	2.95	3.00	0.33	<0.0001
WOMAC physical function sub-scale score					
Baseline	505	43.05	43.00	16.53	<0.0001#
Change from baseline					
Day 5	496	2.55	1.00	0.47	0.148
Day 30	494	10.48	10.00	0.36	<0.0001
Day 60	486	17.00	20.50	0.19	<0.0001
Day 90	485	24.22	27.00	0.32	<0.0001
WOMAC total score					
Baseline	505	60.94	62.00	23.60	<0.0001#
Change from baseline					
Day 5	496	3.96	3.00	0.11	0.066
Day 30	494	15.37	16.50	1.13	<0.0001
Day 60	486	24.25	30.00	0.47	<0.0001
Day 90	485	34.52	40.00	1.41	<0.0001

Friedman test (repeat measures); * Wilcoxon test.

Table 4: VAS scores and change from baseline over 90 days.

Variables	No.	Mean	Median	SD	P (Versus baseline)*
Pain score (0-10 VAS)					
Baseline	505	7.08	7.00	2.27	<0.0001#
Change from baseline					
Day 5	496	1.08	1.00	0.56	0.066
Day 30	494	2.04	2.00	0.44	<0.0001
Day 60	486	2.64	2.00	0.23	<0.0001
Day 90	485	3.42	4.00	0.06	<0.0001

Friedman test (repeat measures); * Wilcoxon test.

Rescue analgesic

Of the total 505 patients rescue analgesic was required for breakthrough pain only for 138 (27.3%) patients. The mean (SD) duration of rescue analgesic use was 15.02 (16.83) days. The need for rescue was similar in males (26.4%) and females (28.1%). However, the need for rescue was lesser in normal weight individuals (17.7%), as compared to overweight and obese patients (30.1%).

Safety

There were no adverse events reported by any of the patients during the study period.

DISCUSSION

OA is the commonest form of arthritis which is associated with poor quality of life due to disability and hampered physical function. Prevalence of OA increases with age and is about 50% in people above 60 years of age.[17] Several systemic factors have been identified as risk factors for OA, and these may act by increasing the susceptibility of joints to injury, by direct damage to joint tissues, or by impairing the process of repair in damaged joint tissue.[18] Local factors are most commonly biomechanical in nature and adversely affect the forces applied to the joint. Certain specific risk factors have been identified including obesity and metabolic disease, age, sex, ethnicity and race, genetics, nutrition, smoking, bone density and muscle function.[18] A systematic review and meta-analysis of the risk factors for the onset of OA of the knee, has reported that there is a consistent strong association between increased BMD (bone mineral density) and the onset of knee OA in women.[19]

Despite several drugs available for pharmacological therapy, there are no curative therapies currently available for OA, and patients in advanced disease often require surgical management. There is a desperate need for effective therapies to decrease disease progression, and achieve symptom relief for pain and stiffness, to improve the quality of life in patients with OA.

In the last few decades, many nutraceutical products like Boswellia, Aflapin, chondroitin sulphate, glucosamine sulphate, collagen peptide, curcumin, fish oil, ginger, green tea, and rosehip extract have been used for treatment of OA of knee but with varied results.[12] These supplements have been found to be effective in knee OA in various studies, and no serious side effects have been reported for any of these supplements.[12] Due to there are significant anti-inflammatory properties, gum resin extracts of *Boswellia serrata* containing 3-O-acetyl-11-keto-β-boswellic acid (AKBA) are a promising potential as therapeutic interventions for inflammatory diseases such as OA.[13] However, the AKBA has poor bioavailability following oral administration. Aflapin is a synergistic composition of *Boswellia serrata* extract enriched in AKBA (3-O-Acetyl-11-keto-beta-boswellic acid) and non-volatile oil portion of *B. serrata* gum resin.[13] Due to this formulation, the availability of AKBA in systemic circulation is increased by 51.78%.[20] In the last two decades, preparations of the gum resin of Boswellia serrata (a traditional ayurvedic medicine) and of other Boswellia species have experienced increasing popularity in Western countries.[23] Animal studies and pilot clinical trials support the potential of *Boswellia serrata* gum resin extract (BSE) for the treatment of a variety of inflammatory diseases like inflammatory bowel disease, rheumatoid arthritis, OA, and asthma. The pharmacological effects of BSE were mainly attributed to suppression of leukotriene formation via inhibition of 5-lipoxygenase (5-LO) by two boswellic acids, 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid (AKBA).[21] These two boswellic acids have also been chosen in the monograph of Indian frankincense in European -pharmacopoeia 6.0. Compared to NSAIDs, it is expected that *B. serrata* may be associated with better tolerability.

UC-II is derived from chicken sternum cartilage and is glycosylated to improve stability.[22] Collagen supplements are rich in amino acids such as glycine, proline, and hydroxyproline; all of which play important roles in the building of joint cartilage and may also have anti-inflammatory and antioxidant effects and have been speculated to act as signalling molecules.[14] Studies have shown that undenatured type II collagen is effective in the treatment of RA and OA.[23,24] A White Paper on collagen hydrolyzates and ultrahydrolyzates in OA reports evidence of efficacy in a few small-scale clinical trials.[25]

In an early study with 40 mg UC-II for 42 days in patients with OA, there was an average reduction of 26% in the pain score.[30] This was observed in 80% patients with OA (4/5), and there were no adverse effects reported by patients.[30] We observed a 15.2% reduction in pain score on day 5 which increased progressively to 48.3% reduction by day 90. Thus, we observed a greater reduction in pain score as compared to Bagchi et al. This greater reduction in pain scores in our study could be probably due to use of aflapin along with UC-II. In a multicenter randomized, double-blind, three-arm, placebo-controlled study, efficacy and tolerability of UC-II was compared with placebo and glucosamine hydrochloride plus chondroitin sulfate (GC) in patients with OA of knee over 180 days.[26] On day 180, the UC-II therapy demonstrated a significant reduction in overall WOMAC score compared to placebo (p=0.002) and GC (p=0.04). Also, there were significant changes for all three WOMAC subscales: pain (p=0.0003 vs. placebo; p=0.016 vs. GC); stiffness (p=0.004 vs. placebo; p=0.044 vs. GC); physical function (p=0.007 vs. placebo). These observations are coherent with our study findings. Safety of UC-II was similar to placebo and GC.[31] Similarly, a randomized comparative clinical trial (Crowley et al) of 90-day therapy with UC-II versus combination therapy with GC (glucosamine and chondroitin sulphate) in OA of knee showed significantly greater reduction in WOMAC score and pain scores with UC-II as compared to GC therapy.[27] We observed a significant improvement in

WOMAC scores for all domains of pain, stiffness and physical function by treatment with combination therapy of orally administered Aflapin and UC-II over a 90-day period. Also, in the study by Crowley et al there were significant reduction in pain scores with UC-II therapy. They reported significant enhancement in daily activities suggesting an improvement in their quality of life with UC-II therapy.[32] In our study we observed a significant reduction of pain scores from 7.08 (2.27) to 6.00 (1.71) on day 5 ($p<0.05$) and 3.66 (2.21) on day 90 ($p<0.0001$). Also, improvement in the mean scores for physical function domain of WOMAC suggests that the quality of life improved with combination therapy of Aflapin and UC-II.

In a double-blind, randomized, placebo-controlled clinical study by Sengupta et al which evaluated the early efficacy of aflapin in 15 subjects with OA of knee, aflapin caused clinically and statistically significant improvements in pain scores and physical function scores.[28] These improvements were recorded as early as 7 days after starting therapy. In another 30-day, double-blind, randomized, placebo-controlled study of aflapin in the management of clinical symptoms of OA of the knee, 60 subjects received either 100 mg (n=30) of Aflapin or placebo (n=30) daily for 30 days.[29] Aflapin provided clinically and statistically significant improvements in pain scores and physical function scores with effects starting as early as 5 days of treatment. We also observed improvement ($p>0.05$) in pain and WOMAC scores on day 5 after starting the combination therapy with aflapin and UC-II. In our study we also observed significant improvements in pain scores and WOMAC scores on day 5 after starting the combination therapy with aflapin and UC-II. The combination of aflapin and UC-II could be additive for the therapeutic effects due to different mechanisms of each ingredient. Aflapin, can provide powerful anti-inflammatory efficacy and anti-arthritic actions, whereas UC-II can provide basic elements required for building of joint cartilage. UC-II also has antioxidant and anti-inflammatory actions which could potentiate the effects of aflapin.

The common adverse effects reported by Crowley et al were gastrointestinal (5/26) and musculoskeletal (7/26) observed in 16/26 (61.5%) patients on UC-II therapy.[32] Sengupta et al reported no change in safety parameters including laboratory parameters with aflapin therapy. However, in our study none of the patients reported any adverse effects after starting therapy with aflapin and UC-II.

This post-marketing clinic-based study captured the real-world safety and efficacy data of use of capsules containing Un-denatured type II collagen 40 mg and Aflapin 100 mg administered for 90 days for treatment of OA of knee. Being devoid of potential adverse effects, such as gastric ulceration and cardiovascular toxicity, UC-II and aflapin combination can offer a valuable therapeutic option for the management of knee OA. The well-established safety profile of both ingredients can show their potential for clinical use.

Our study has some limitations in terms of being a post-marketing study. Due to the observational study design, strict control of confounding factors could not be obtained. Hence, this limits the extrapolation of study results to large scale population.

CONCLUSION

The excellent safety and efficacy profile of UC-II and aflapin combination makes it a desirable pharmacological treatment modality for management of patients of knee OA.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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