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Efficacy of Plant-Extract Based Oil-Blends for Osteoarthritis of Knee: Randomized, Double Blind, and Placebo Controlled Study

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Abstract

Background: Osteoarthritis is the most common degenerative joint disease. This study has focus on osteoarthritis (OA) of knees which primarily affects the elderly causing functional impairment and disability. There are no interventions that can completely reverse the disease progression by restoring degraded cartilage; however, symptoms can usually be effectively managed with lifestyle changes, physical and other therapies, medications, and surgery. Further, the existing studies have evaluated benefit of single herb or its essential oil towards treatment of OA pain or a symptom.

Objective: The proposed polyherbal oil (referred as test product) is a unique synergistic oil blend prepared using novel concept of Ayurveda Plant Nanocellopathy, as elaborated in the Sarangdhar Samhita, that blends therapeutic plant extracts/ oils to derive maximum benefit from the herb extracts/ oils having soothing, analgesics and anti-inflammatory properties. The objective of this study is to validate the efficacy of the topical use of the test product in treatment and control, and stopping or delaying progression of knee OA in comparison with the placebo.

Method: A randomized, double blind, parallel group, placebo controlled comparative study with 200 adult participants having OA of the knee was conducted. The participants who fulfilled the inclusion criteria were allocated between two study arms (test and placebo) in the ratio of 1:1 using randomization. The efficacy of the test product was measured as a decrease or negative change in VAS as well as WOMAC Index scores. Progression of OA, or regression of it was assessed radiographically by comparing the post and pre-treatment X-rays measured on K & L grade and joint space narrowing results. The safety of the test product was assessed in terms of adverse events, if any.

Findings: The decrease in the WOMAC Index score and VAS-POM score in test group was observed on a continuous basis, that is, from baseline to day 30 and then decreasing in subsequent follow-up visits on day 60 and day 90, suggesting that continuous use of the test product was beneficial to provide relief from symptoms. Significantly fewer participants with K & L grade >1 using test product showed progression in OA as compared to the placebo group. The test product did not result in any adverse events indicating safety of the oil use.

Conclusion: Topical application of test product is found effective in relieving the symptoms of knee OA and stopping progression of knee OA without any reported side-effects.

Keywords: Knee; Osteoarthritis; Polyherbal oil blend; Topical application; Natural; WOMAC index; VAS-POM; K & L grade; Joint space narrowing (JSN)

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Introduction

Arthritis is a general term that means inflammation of the joints. Osteoarthritis, commonly known as wear and tear arthritis, is the most common type of arthritis. It is associated with breakdown of cartilage in joints and can occur in almost any joint in the body. It commonly occurs in the weight-bearing joints of hips, knees, and spine. It also affects the fingers, thumb, neck, and large toe. Osteoarthritis (OA) usually does not affect other joints unless previous injury, excessive stress or an underlying disorder of cartilage is involved. Cartilage is a firm, rubbery material that covers the ends of bones in normal joints. Its main function is to reduce friction in the joints and serve as a "shock absorber". Osteoarthritis causes the cartilage in a joint to become stiff and lose its elasticity, making it more susceptible to damage. Over time, the cartilage may wear away in some areas, greatly decreasing its ability to act as a shock absorber. As the cartilage deteriorates, tendons and ligaments stretch, causing pain. If the condition worsens, the bones could rub against each other [1-8].

OA is the most common degenerative joint disease, affecting more than 25% of the population above 18 years-old [2]; the chance of developing the disease increases with age [1]. It primarily affects the elderly causing functional impairment and disability [1,3-5,7]. Most people above 60 years of age have OA to some degree, but its severity varies [1]. According to World Health Organization (WHO) 9.6% of men and 18.0% of women aged above 60 years have symptomatic osteoarthritis worldwide. 80% of those with osteoarthritis have limitations in movement, and 25% cannot perform their major daily activities of life [9]. Epidemiological observations show that after the age of 50, OA particularly of the knee, is more common in women than in men, suggesting that estrogen deficiency may play a role in the onset or progression of this condition [1,7]. Even people in their 20s and 30s can get OA, although there is often an underlying reason, such as joint injury or repetitive joint stress from overuse [1].

Osteoarthritis affects an estimated 27 million Americans [1,5]; it is the second most common rheumatologic problem and the most frequent joint disease with a prevalence of 22% to 39% in India [9,10]. The prevalence of OA is increasing due to population ageing and an increase in related factors such as obesity, sedentary life style. The physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity [9].

Symptoms of OA most often develop gradually and include [1,2,4-6]: Joint aching and soreness, especially with movement; pain after overuse or after long periods of inactivity; stiffness after periods of rest; bony enlargements in the middle and end joints of the fingers (which may or may not be painful); and joint swelling. Pathologically, OA is characterized by progressive loss of articular cartilage and new bone formation, identified on conventional radiography. However, it is increasingly apparent, based on pathological, magnetic resonance imaging (MRI) and arthroscopy studies, that progressive OA involves all joint tissues including bone marrow lesions, degeneration of ligaments formation of osteophytes synovial proliferation and variable degrees of inflammation, fat pad inflammation, and high subchondral bone turnover [2,8].

The etiology of OA is multi-factorial that increase a person's chances of developing OA [1,2,5]. These include:

1. **Aging:** One of the most common risk factors for OA is age. A majority of people above the age of 65 were diagnosed with radiographic changes in one or more joints. In addition to cartilage, aging affects other joint tissues, including synovium, subchondral bone and muscle, which is thought to contribute to changes in joint loading [2].
2. **Heredity:** Some people have an inherited defect in one of the genes. This causes defective cartilage, which leads to more rapid deterioration of joints. People born with an abnormality of the spine (such as scoliosis or curvature of the spine) are more likely to develop OA of the spine.
3. **Obesity:** Obesity increases the risk for OA of the knee, hip, and spine. Maintaining ideal weight or losing excess weight may help prevent OA of these areas or decrease the rate of progression once OA is established.
4. **Injury:** Injuries contribute to the development of OA. For example, athletes who have knee-related injuries may be at higher risk of developing knee OA. Similarly, people who have had a severe back injury may be predisposed to develop OA of the spine. People who have had a broken bone near a joint are prone to develop OA in that joint.
5. **Joint overuse:** Overuse of certain joints increases the risk of developing OA. For example, people in jobs requiring repeated bending of the knee are at increased risk for developing OA of the knee.
6. **Other diseases:** People with rheumatoid arthritis, the second most common type of arthritis, are more likely to develop OA. Certain rare conditions, such as iron overload or excess growth hormone, increase the chance of developing OA.

Keeping in consideration the symptoms and causes, the diagnosis of OA is based on a combination of the following factors [1,11]: description of symptoms such as pain, stiffness and functional limitation (as listed in The Western Ontario and McMaster Universities Osteoarthritis Index - WOMAC) helps evaluate the condition of patients with OA [12]; the location and pattern of pain; physical examination to check for tenderness, swelling or redness, and for range of motion in the affected joint [11]. Radiological examinations like X-rays help to confirm the diagnosis and eliminate possibility of another types of arthritis. X-rays show how much joint damage has occurred. In early detection cases or in situation where the X-ray results are inconclusive, magnetic resonance imaging (MRI) may help to get a better look at the joint and surrounding tissues [1,11]. In some cases, blood tests are performed to determine any form of arthritis.

Since the molecular mechanisms involved in OA initiation and progression remain poorly understood, currently there are no interventions to restore degraded cartilage or decelerate disease

progression [2]. The aim of OA treatment normally is to reduce pain, improve physical function, prevent disability, and enhance the quality of life over the short term [8]. OA usually is treated by a combination of treatments, including exercise, weight loss if needed, medications, physical therapy with muscle strengthening exercises, hot and cold compresses to the painful joint, removal of joint fluid, injection of medications into the joint, and use of supportive devices such as crutches or canes. Surgery may be helpful to relieve pain when other treatment options have not been effective [1,3,6,11].

The treatment form depends on several factors, including age, activities and occupation, overall health, medical history, OA location, and severity of the condition [1]. Common medications used for providing relief primarily from OA pain include [1,11] the following:

1. Acetaminophen (Tylenol, others) has been considered effective for people with OA having mild to moderate pain. However, taking more than the recommended dosage of acetaminophen can cause liver damage.
2. Over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve, others) help to relieve OA pain. Prescribed stronger NSAIDs may also slightly reduce inflammation along with relieving pain. NSAIDs can cause stomach upset, cardiovascular problems, bleeding problems, and liver and kidney damage. Topical NSAIDs and some medications in the form of creams, rubs, or sprays may be applied over the skin of affected areas to relieve pain and have fewer side effects.
3. Duloxetine (Cymbalta) is used as an antidepressant, however is also approved to treat chronic pain, including OA pain.

In situations of persistent pain, not relieved with pills and gels, steroids can be injected directly into the joint several times a year. However, some experts believe that these may ultimately accelerate joint damage. When OA pain is severe, stronger pain pills, such as narcotics are also suggested. Unfortunately, pain killers do not reverse or slow the progression of joint damage caused by OA. When pain interferes with normal activities, then surgery may be recommended which although effective, is a costly and painful alternate [1,11].

Complementary treatment for OA

There are various complementary and alternative medicines (CAM) as a cost-effective and promising means to answer OA symptoms [11]. CAM treatments that have shown promise for OA include:

1. Some studies indicate that acupuncture can relieve pain and improve function in knee with OA. In acupuncture treatment, hair-thin needles are inserted at specific points on the body.
2. Glucosamine and chondroitin are nutritional supplements and studies have shown mixed results towards effect of these for OA. A few studies have indicated benefits, while most indicate that these supplements are not better than a placebo. Further, glucosamine and chondroitin may interact with blood thinners such as warfarin and cause bleeding problems.
3. Avocado-soybean unsaponifiables is a nutritional supplement, which is a mixture of avocado and soybean oils. It is widely used in Europe to treat knee and hip OA. It acts as an anti-inflammatory, and some studies have shown its effect to slow down or even prevent joint damage.
4. Herbal treatment has also been found successful in relieving pain and discomfort of OA. It includes traditional Chinese medicine, Unani, Ayurveda and aromatherapy [7,8,13-17].
5. Herbal oils or essential extracts/oils can be used in different ways, including massage, bathing, and inhalation. The exact mechanism of how aromatherapy relieves pain is unclear. It is believed that the scent from aromas activates olfactory nerve cells, which result in limbic system stimulation [18]. The properties of the oils, the fragrance, and its effects, may determine both psychological and physiological effect. When used in massage, the oils are absorbed through the skin and penetrate the tissues [19,20]. Use of such herbal and plant extracts/ oils in managing symptoms of OA has been widely accepted across the world. However, most of the claims have not always been backed up by scientific researches. There are limited studies done with animal models and with controlled clinical human trials. Some of the oils that have shown promising results to reduce pain and other OA symptoms are ginger oil, peganum, fish oil, krill oil, argan oil, sesame oil, shea nut, *Nigella sativa,* lavender, chamomile and extracts of *Curcuma longa* [13,21-30].

Study rationale

As indicated above, there are no interventions that can completely reverse the disease progression by restoring degraded cartilage; however, symptoms can usually be effectively managed with lifestyle changes, physical and other therapies, medications, and surgery [2,11]. Medications such as Acetaminophen, NSAIDS and Duloxetine are often prescribed to patients for reducing pain. However, these drugs can have serious side effects. Therapies and Surgeries are also recommended, but they are labor-intensive, and are not cost-effective [1,6,11]. Further, the existing studies have evaluated benefit of one herb and/or its essential oil at a time towards treatment of OA pain or a symptom. It would be highly beneficial if positive effects of multiple herbs and their extracts/oils can be pooled in one formulation. Mixing herbs and their extracts or oils requires precision; there may either be an antagonistic effect or synergistic effect [31].

The proposed polyherbal oil (referred as test product) is a unique synergistic oil blend containing extract/oil of *Gaultheria procumbens* (Wintergreen), *Lavandula angustifolia* (Lavender),

Aniba rosaeodora (Rosewood), *Anthemis nobilis* (Roman Chamomile), *Eucalyptus globulus* (Eucalyptus), *Rosmarinus officinalis* (Rosemary) and *Mentha piperita* (Peppermint), *Syzygium aromaticum* (Clove), *Ocimum basilicum* (Basil) and Select Citrus extracts/oils, Sesame and Mustard oils. It is prepared using novel concept of Ayurveda Plant Nanocellopathy, as elaborated in the Sarangdhar Samhita that blends therapeutic plant extracts/oils in a form to derive maximum benefit through a trans-dermal delivery mechanism. Given the novelty of the proposed polyherbal oil blend, the focus of this paper is to scientifically establish the efficacy of the test product in treating OA of the knees and its symptoms. Also a secondary objective is to note any adverse reactions to the test product.

In consideration of the proposed polyherbal novel formulation, the objective of this study is to validate the efficacy of topical use (unlike a massage, just a few drops are rubbed in for 15 seconds on the affected knees) of a few drops of the test product (natural plant extract-based oil blend) in treatment and control of knee OA, and in stopping or delaying progression of OA, in comparison with the placebo. The placebo is a fragrant coconut oil. Further the safety of the test product is evaluated in terms of any acute reaction/allergies manifestation subsequent to application of the test product.

Research Methodology

Study design and participants

A randomized, double blind, parallel group, placebo controlled comparative study was performed in accordance with the ethical principles that have their origins in the Declaration of Helsinki in Seoul, 2013 and EC notifications were made as per Good Clinical Practice (GCP) Guidelines issued by Central Drug Standard Control Organization and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research, Government of India. The clinical trial was registered with the Clinical Trial Registry of India (CTRI) number CTRI/2018/10/016235.

A total sample size of 200 participants (including anticipated drop outs) was arbitrarily selected at the specified investigation centre, without bias, following a complete screening of all inclusion and exclusion criteria. The sample size was assessed at the confidence level 95% and test power 80%. The enrolled participants were subjected to randomization as per the randomization list and allocated in a 1:1 ratio into test group and placebo group. This was a double blind study where neither the participants nor the investigators were aware of the treatment group assigned. Study duration was 4-5 months with enrolment and baseline interview at day 0; and follow-up at day 30, day 60 and day 90. A window period of +/- 2 days was allowed for follow-up visits.

At screening, questionnaires completed by the participants provided investigator with information on their medical and OA history, and demographics. Pain level in the last week was evaluated using the Visual Analog Scale (VAS) (0 = no pain; 100 = severe pain), and functionality in activities of daily living was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The study included adult participants of either gender, aged ≥ 35 to 80 years, radiographically diagnosed with osteoarthritis (OA) of knees. The further inclusion criteria were: female participants with a negative pregnancy test; pre-randomization score of 40 to 90 on the WOMAC Index; a signed written consent for participation in the study and to undergo a baseline interview; need to return for assessment visits for evaluation; and were not to take any new herbal supplement and prescription or non-prescription medications that has not been recommended by the study physician.

The participants were excluded from the study, if: were with rheumatoid arthritis, fibromyalgia, recurrent or active pseudo-gout, cancer, or other serious medical conditions; single or married female participants were pregnant or have borne children in past one year; with a history of kidney or liver failure or having asthma requiring use of corticosteroids or use of oral corticosteroids within the past 4 weeks; with a history of intra-articular knee depo corticosteroids within the previous 3 months, or intra-articular hyaluronate within the previous 6 months; with evidence or history of medical or surgical event in the past year that may significantly affect the study outcome such as arthroscopy of the knee within the previous year; significant injury to the knee within the previous 6 months; or a rash or open wound over the knee; reporting use of prescription or non-prescription drugs that has not been pre-approved by the study physician; with known allergies to the main components of the test product or placebo; participation in another clinical trial or taking an investigational product in the past three months; and if any participant who is not able to give informed consent.

A participant was excluded during follow-up visit if: has recently developed and diagnosed with any major systemic, immunological, gastrointestinal disease; any female participant who became pregnant; reporting use of restricted medication during the study period; has developed allergies to the main components of the test product; and who was not able to give adequate informed consent or did not appear for the first follow up visit.

Participants were informed that they were free to withdraw from the study at any time without stating the reason. Only a participant whose data is complete for all the observations is considered to have completed the study. However, the investigator could withdraw a participant from the study for following reasons: serious adverse event; protocol violation; consent withdrawal, not due to an adverse event; migration from the study site; lost to follow-up; or any other relevant reason which may intervene in the conduct of the study.

Procedures

The participants were informed about the study, and on agreement, signed the informed consent form and were screened for applicable enrolment criteria. The informed consent process of individual participants, including the procedure of providing information to the participants, their understanding on such consent and the signed consent form, were maintained by the investigator for record. Eligible participants were screened and

enrolled during the baseline visit (day 0). A baseline interview was conducted to collect demographic data, medical history, prior and current medications, and OA history. Level of Pain-on-movement (POM) was assessed using the VAS, and current level of pain in executing daily activities was assessed using the WOMAC - a series of 5 questions pertaining to the amount of pain the participant is currently experiencing. WOMAC questionnaire pertain to the amount of pain the participant is currently experiencing when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'At night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)] and assessed on 5-point Likert scale (i.e., 'None'=0; 'Mild'=1, 'Moderate'=2; 'Severe'=3; 'Extreme'=4).

In addition, the efficacy of test product in stopping/delaying the progression of OA was also studied. Progression of OA, or absence of it, was assessed radiographically by comparing the post and pre-treatment X-rays. Based on Kellgren and Lawrence (K & L) five-grade radiographic classification scheme for OA, also known as K & L grade, a radiographically established OA is defined. The K & L index is calculated by assessing joint space narrowing (difference between joint space width between two visits), osteophyte formation and deformity at bony ends. Therefore, progression of OA can be assessed by measuring joint space narrowing (JSN) and increase in the overall K & L grade on follow-up visit; a joint space narrowing (JSN) of ≥1 mm and of ≥1.5 mm at follow-up and an increase of minimally 1 grade of Kellgren and Lawrence is clinically diagnosed as progression of OA.

Most commonly, five-grade radiographic classification scheme for OA (0 to 4, grade 0= no OA and grade 4= severe OA) as described by Kellgren and Lawrence (KL) in 1957, is employed to grade the OA radiographically [32,33]. X-rays or radiographs are examined for joint space narrowing, osteophyte formation and deformity at bony ends. Description of the grade is as follows: Grade 0= no OA; Grade 1= doubtful narrowing of the joint space with possible osteophyte formation; Grade 2= possible narrowing of the joint space with definite osteophyte formation; Grade 3= definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends; and Grade 4= large osteophyte formation, severe narrowing of the joint space with marked sclerosis, and definite deformity of bony ends [32,33].

Participants were randomized to receive either the test or the placebo products with instructions to apply them. Briefly, the participants were advised to apply few drops of oil and rubbed in for 15 seconds with fingertips on and around the knee (into the affected area) twice a day, for 3 months. Participants were re-evaluated with respect to their knee health during follow-up (assessment) visits on day 30, 60 and 90. Safety analyses was done by recording allergic reaction, adverse events and severe adverse events based on history and physical examination on day 30, 60 and 90. An AE is defined as any unfavourable and unintended sign, symptom or disease, whatever their nature, severity, seriousness, and the supposed role (causality) of the product administered or the experimental procedure.

According to the inclusion and exclusion criteria, no other medicine (herbal/allopathic/other alternative medicine) were taken by the participants. The use of any incidental medication (e.g. thyroid medication, antipyretic medication etc.) was recorded. In case if any other medication is administered to the participant during the course of the study, the decision to continue or discontinue the participant was taken by the investigator. Vital examination (axillary temperature, heart rate and respiratory rate) and clinical examination (including general physical and systemic examination) were done on each visit day and on any unsolicited follow up visit or at any time during the conduct of study, if deemed necessary.

Outcomes

Efficacy of the test product was measured by assessing improvement in symptoms of OA of knee before and after commencement of the treatment. Efficacy assessments were made according to the following:

1. A decrease or negative change in WOMAC scores from baseline indicating improvement of symptoms and limitations, as compared to the placebo (WOMAC assesses pain, stiffness and physical functional disability using a series of 5 questions)
2. A decrease or negative change in the VAS score assessing pain-on-movement (POM)
3. Absence of OA progression as per radiological assessment based on X-rays done both at baseline and at the end of the treatment

Statistical analysis

Student's t-test, 2 way repeated measures ANOVA and Chi-square test were employed to analyse different data. All p-values reported are based on 2-sided tests and p-values <0.05 were considered to be significant. Descriptive statistics for age, BMI (body mass index) and gender distribution at enrolment was calculated for the entire study population and each group. To assess the efficacy of the test product, improvement in pain, movement and functionality, before and after treatment were assessed as per the study protocol and summarized as mean score ± SD and respective p-value. Mean as a measure of central tendency and standard deviation (SD) are used for data analysis because these utilize all data and are also a good representative of data. Repeated samples from the same population can also be well compared with mean scores. Similarly, SD provides a more accurate understanding about the distribution of data because SD increases with the increase in dispersion of data. These measures also provide comparative understanding between two test groups. Composite WOMAC Likert pain score (pain score = 0 to 20), and Pain on movement (POM) as assessed by a 100 mm Visual Analog Scale (VAS; 0= no pain and 100= severe pain), determined by the participants' responses. X-rays done both at baseline and at the end of the treatment were compared to evaluate the absence of progression in OA of knees based on five-grade radiographic classification scheme for OA given by K & L.

The safety of the test product was evaluated by assessing if there is any adverse event, such as acute/allergic reactions that manifested or exacerbated subsequent to interventions. Incidences of local and systemic, solicited or unsolicited AEs occurring were noted, if any.

Results

A total of 200 participants were enrolled in the clinical trial (100 in each group). 100 participants in each of the two groups (test and placebo group) were subjected to baseline interview. No participant was lost to follow up or withdrawn from the study. Demographic characteristics of each group are shown in **Table 1**. The average age of participants belonging to the placebo group was 58.76 ± 9.09 years, while that of test group was 60.40 ± 9.97 years (P>0.05, non-significant). The gender distribution in test group was well-balanced, with 45/100 (45%) female participants as compared to 55/100 (55%) male participants. However, the number of male participants in the placebo group was significantly higher (68/100) as compared to the female patients (32/100). Overall, 77/200 (38.5%) females and 123/200 (61.5%) males participated in the study. The average BMI of the participants in both groups was comparable (Test Group: 25.4 ± 2.44 Kg/m^2 and Placebo: 26.72 ± 3.63 Kg/m^2).

The outcome of the study was based on self-assessment of the participants with respect to level of pain-on-movement (POM), measured using VAS (0=no pain and 100=severe pain) and difficulty in executing daily activities as measured by the WOMAC index. The VAS-POM and WOMAC index was calculated at baseline and each follow-up visit, that is day 30, day 60 and day 90. **Table 2** tabulates the Composite WOMAC Index (sum of the scores from all 5 questions) and the VAS-POM for the baseline and each assessment visits. At baseline the composite WOMAC score for the participants in test group was 8.11 ± 1.01 and the placebo group was 10.49 ± 1.55. The VAS-POM score for the participants in test group was 54 ± 8 and placebo group was 48 ± 15.

A significant and continuous decrease of the WOMAC score and VAS-POM score was observed in the test group at each assessment visit as compared to baseline, suggesting that continuous use of the test product provided relief from the main symptoms of OA of the knee (**Table 2**). In contrast, the placebo group saw a significant increase in the WOMAC score as well as VAS-POM score. At the end of the study (day 90)**,** a negative change in the WOMAC score (-4.86 ± -0.025) and VAS-POM score (-34.56 ± -4.08), when compared to baseline, was observed for the test group; this was significantly different from placebo group which saw a positive change indicating increase in pain and difficulty in executing daily activities.

In the study, as per the inclusion criterion, all participants had radiographically established OA. Both knees were analyzed for progression of OA, subsequent to usage of the test product and placebo for 3 months, in all the participants (100 in each group); therefore, number of joints analyzed for each group was 200. In test group, 53/200 participants had a K & L grade = 1 and 147/200 had a K & L grade >1 (indicating progressive OA); the participant distribution was comparable with the placebo group (K & L grade = 1: 48/200 and K & L grade >1: 152/200). Joint space narrowing (JSN) was measured for all the participants **(Table 3)**. In test group, out of 53 participants with K & L grade = 1, 3 (5.66%) participants had a JSN of ≥ 1 mm and 2 (3.77%) had a JSN ≥ 1.5 mm whereas in the placebo group, out of 48 participants with K & L grade = 1,

Table 1 Summary of demographics of the study participants.

Variables	Test Group	Placebo Group	Total
Sample size (N)	100	100	200
Age (years)			
Mean	60.40	58.76	59.58
SD	9.97	9.09	9.53
Gender			
Female	45 (45%)	32 (32%)	77 (38.5%)
Male	55 (55%)	68 (68%)	123 (61.5%)
BMI (Kg/m^2)			
Mean	25.40	26.72	26.06
SD	2.44	3.63	3.03

Table 2 Composite WOMAC and VAS-POM score on Day 0, 30, 60, 90 with mean change in scores.

Variables	Test Group [Mean (SD)]	Placebo Group [Mean (SD)]	*P*-value
Sample Size	**100**	**100**	
Composite WOMAC Score			
Baseline	8.11 (1.01)	10.49 (1.55)	<0.0001
Day 30	7.57 (1.56)	12.34 (1.62)	
Day 60	3.55 (0.84)	14.03 (1.9)	
Day 90	3.25 (0.81)	15.27 (1.7)	
Mean change from baseline to day 90	-4.86 (-0.205)	4.78 (0.18)	
VAS - POM (Pain-on-movement)			
Baseline	54 (8)	48 (15)	<0.0001
Day 30	48 (7)	58 (16)	
Day 60	23 (5)	66 (16)	
Day 90	19 (4)	75 (16)	
Mean change from baseline to day 90	-34.56 (-4.08)	26.51 (1.36)	

5 (10.4%) participants had a JSN of ≥ 1 mm and 7 (14.58%) had a JSN ≥ 1.5 mm **(Table 3)**. 4/53 (7.54%) participants in test group and 8/48 (16.66%) participants in the placebo group showed increase in K & L grade. Even though the difference between test group and placebo is not significant, the trend is apparent; fewer participants in test group showed signs of progressive OA as compared to the placebo group whereas 49 participants have shown no progression in OA. Similar results were observed in participants with K & L grade >1. It is noteworthy, that significantly fewer participants with K & L grade >1 using test product showed progression in OA with JSN ≥1 mm as compared to the placebo group [Test:4/147 (2.72%) and placebo:13/152 (8.55%)], which indicates that test product is effective in stopping the progression of OA of knees. The results are also evident with comparison of X-ray film pictures during pre-treatment and post-treatment by the test product. JSN can be identified in X-ray during pre-treatment phase while improvement can be seen in X-ray after treatment with test product **(Figures 1a, 1b, 2a and 2b)**.

All 200 participants were included in the safety analyses. No adverse event was reported. In other words, the test product did not result in any allergies or any other side effects.

Table 3 Comparing progression of OA by measuring the changes in K & L grade and JSN in both groups after 3 months of oils usage.

Variables	Test Group	Placebo Group	*P* value (Chi-squared test)
Number of participants (Number of joints)	100 (200)	100 (200)	Not Significant
K & L grade= 1 [at day 0]	53 (26.5%)	48 (24%)	Not Significant
JSN ≥1 mm (%) [after 3 months]	3 (5.66%)	5 (10.41%)	Not Significant
JSN ≥1.5 mm (%) [after 3 months]	2 (3.77%)	7 (14.58%)	P=0.058
Increase in K & L (%) [after 3 months]	4 (7.54%)	8 (16.66%)	Not Significant
K & L grade >1 [at day 0]	147 (73.5%)	152 (76%)	Not Significant
JSN ≥1 mm (%) [after 3 months]	4 (2.72%)	13 (8.55%)	Significant
JSN ≥1.5 mm (%) [after 3 months]	3 (2.04%)	5 (3.28%)	Not Significant
Increase in K & L (%) [after 3 months]	5 (3.4%)	12 (7.89%)	Not Significant

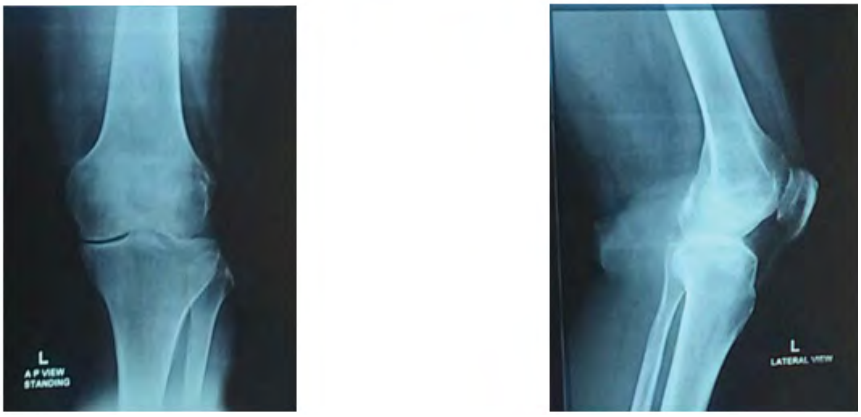

Figure 1 (a and b) X-ray pictures showing clear joint space narrowing during pre-treatment by the test product.

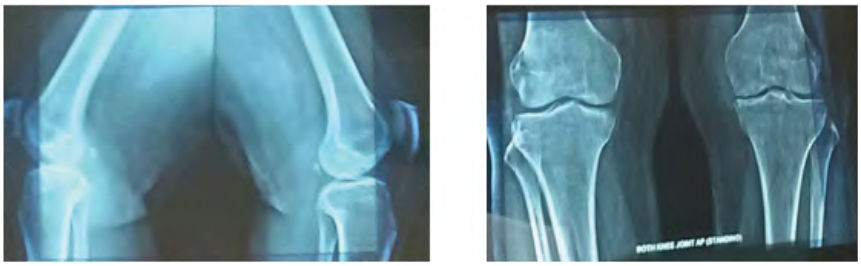

Figure 2 (a and b) X-ray pictures showing improvement in joint space narrowing after treatment with the test product.

Discussion

Osteoarthritis (OA) is the most common degenerative joint disease. There are no interventions that can completely reverse the disease progression by restoring degraded cartilage; however, symptoms can usually be effectively managed with lifestyle changes, physical and other therapies, medications, and surgery [2,11]. Prescribed medications, besides reducing pain, can have serious side effects such as stomach upset, cardiovascular problems, bleeding problems, and liver and kidney damage. Therapies and Surgeries are also recommended, but they are labour-intensive, not cost-effective and take time [1,6,11]. Use of essential oils derived from plants, have been in use, since ancient times, for relieving pain [18-20]. Multiple essential oils are known to possess analgesic and anti-inflammatory properties. Oil massages with essential oils/plant extracts are known to excretes endorphins and increases neurotransmitter serotonin into the plasma, that reduces stress levels and promotes parasympathetic activation which blocks pain [18-20]. Uses of essential oils in relieving symptoms of OA have not only been recommended anecdotally but have also been researched clinically. Massaging the affected area with essential oils such as Ginger oil, peganum, fish oil, krill oil, argan oil, sesame oil, shea nut, *Nigella sativa*, lavender, chamomile and extracts of *Curcuma longa* has shown to reduce pain and other OA symptoms [13,21-30]. However, most of the studies have evaluated benefit of one essential oil at a time.

In the current study, the efficacy of the test product, which is a synergistic polyherbal blend of extracts/ oils, is assessed in the

treatment of symptoms of OA in knee. Main symptom of OA normally is pain-on-movement (POM) and pain in executing daily activities such as standing, walking or climbing stairs. The efficacy of the test product was measured as a decrease or negative change in VAS as well as WOMAC Index scores towards these symptoms. Based on the participants' responses in both the group at baseline and follow-up visits scheduled on day 30, 60 and 90, it was observed that participants using test product experienced a significant decrease in the symptoms of OA from the onset of the study, as measured by WOMAC Index and VAS-POM **(Table 2).** This relief in symptoms of knee OA was not observed in the placebo group; instead, placebo group participants reported increased pain and difficulty in daily activities.

Additionally, the decrease in the WOMAC Index score and VAS-POM score in test group was observed on a continuous basis, that is, from baseline to day 30 and then decreasing in subsequent follow-up visits, suggesting that continuous use of the test product was beneficial to provide relief from symptoms **(Table 2).** In case of test product, VAS-POM scores indicate that there was decrease in pain score by 11.11% from day 0 to day 30, further effective decrease in pain score by 47.5% from day 30 to day 60, and 22.17% decrease in pain score from day 60 to day 90. The pain score dropped by 57.4% from day 0 to day 60 and significant overall 64.81% decrease in pain was observed from day 0 to day 90. Similarly, test product resulted in providing comfort to the participants according to WOMAC scores. On the other hand, participants who were non-users of the test product (that is placebo group) had experienced no relief in symptoms as measured both by VAS and WOMAC scores.

The radiographical assessment of OA after 3 months of treatment; fewer participants using test product showed signs of OA progression, as measured by changes in joint space narrowing and overall Kellgren and Lawrence (K & L) grade, as compared to the placebo treatment. It is evident from K & L grades after treatment that the test product is effective in stopping the progression in OA of knees. Further, keeping in consideration the baseline characteristics, it is noteworthy that the BMI of the participants at baseline **(Table 1)** were in the overweight range (> 24.9 Kg/m^2). Obesity has been shown to increase the risk for OA of the knee, hip, and spine and maintaining ideal weight or losing excess weight may help to prevent OA of these areas or decrease the rate of progression in OA (1,2,5). Absence of any adverse event ratifies the safety of the test product treatment. Additionally, participants also found that test product was non-sticky, non-staining and quick to absorb.

Conclusion

This study has evaluated the efficacy of test product, a polyherbal blend of plant extracts/oils in the treatment of knee OA, in comparison to the placebo product. It was observed that number of participants exhibiting symptoms of knee OA showed significant improvement, comparable to the placebo group. Based on physical examinations and participants' responses on WOMAC questionnaire, that evaluate pain and functional limitation experienced by participants in performing daily activities like resting, standing, sitting, climbing stairs and walking, due to pain, stiffness and inflammation of the joints, it can be concluded that application of the test product is effective in reducing symptoms of OA of knee. It shows that continuous application of the product results in decreased pain-on-movement (assessed by VAS), thereby increasing range of motion, finally resulting in ease in performing daily activities. The test product has also shown positive results towards near absence of progression in knee OA according to K & L grade and JSN results. Further, there were no adverse events or side effects in the test group. It can be concluded that topical application of test product is effective in not only relieving the symptoms of knee OA but also protecting knees from progression in OA without any reported side-effects. However, in future research larger samples can be considered for broader and deeper studies which may help to understand different mechanisms of improvement in joint health and in regression of OA. A longer duration study could help to identify the long term effects on joint health with the added view to see the oil-blend impact on reducing or even eliminating the chances of knee replacement. The polyherbal test product could also be put to test for examining its impact on different joints and their health. Such studies in future could improve the understanding of impact of plant extract based poly herbal compounds on joint structures, pain points and other co-related areas.

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