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EFFICACY AND SAFETY OF DR. ORTHO OIL IN THE TREATMENT OF JOINT PAIN, STIFFNESS, AND INFLAMMATION: AN OPEN-LABEL, NON-RANDOMISED CLINICAL STUDY

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ABSTRACT

Background: Joint pain or inflammation is a common complaint among the elderly and is conventionally treated with steroidal or non-steroidal anti-inflammatory drugs (NSAIDs). Because of the adverse effects of these drugs, the present herbal formulation is being developed for the long-term control of pain and inflammation. Objective: The objective of this study was to assess the efficacy and safety of Dr. Ortho Oil in patients with knee pain, low back pain, joint stiffness, sports injuries, and joint inflammations. Methods: This was a single-centre, open-label, non-randomised study. 120 participants were selected based on the inclusion and exclusion criteria. All individuals were instructed to use Dr. Ortho Oil for 60 days. The primary outcome was a change in the frequency of subjects with a significant reduction in joint pain, stiffness, and inflammation. Secondary outcomes were improvements in investigator assessment scale (IAS) and subject self-assessment questionnaire (SAQ) scores at successive administrations compared with the baseline. Results: The study indicated that topical use of Dr. Ortho Oil for 30 days reduced all dimensions of pain. SAQ and IAS scores also decreased significantly ($p<0.0001$) at the end of the study. No adverse or severe adverse events were observed after 30 days of treatment. Conclusion: Dr. Ortho Oil had excellent benefits in decreasing joint pain, stiffness, and inflammation without causing adverse consequences. Dr. Ortho Oil is, therefore, a clinically effective and safe alternative topical treatment for joint pain, stiffness and inflammation.

Keywords: Dr. Ortho Oil, Joint Pain, Inflammation, Clinical Study, Safety.

INTRODUCTION

Inflammation is a sequence of events triggered by noxious stimuli, infection, overactive immune functions, trauma, or injury.[1] It is characterised by pain, swelling, redness, warmth, and loss of function and is achieved through enzyme activation, the release of inflammatory mediators, cell migration, tissue degradation, and repair processes.[2] In modern medicine, the pain and inflammation are most widely treated with steroidal drugs or non-steroidal anti-inflammatory drugs (NSAIDs), which mainly target one specific pathway, such as the inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes that are involved in the biosynthesis of inflammatory mediators such prostaglandin (PGE) and thromboxane.[3] Besides their significant contribution to managing pain and inflammatory conditions, these pharmacotherapies are also associated with significant toxic side effects at different levels, including allergic reactions, gastrointestinal bleeding, acute liver failure, renal toxicity, cardiovascular events, dizziness, nausea and vomiting as well as further damaging joints and tissues.[4,5] Therefore, developing new alternative therapies with analgesic and anti-inflammatory potential is of great clinical significance in treating various pain and inflammatory conditions with minimal or no adverse effects.

Recently, interest has increased in using medicinal plants to treat chronic pain and other inflammatory conditions. For centuries, medicinal plants have been widely used in crude form or as pure isolated compounds to treat various ailments, including inflammation.[1] Ayurvedic medicine, in particular, uses medicinal herbs as a traditional therapy for several inflammatory disorders, including pain, migraine, muscle stiffness, and injuries affecting bones, ligaments, cartilage, and arthritis.[6] Medicinal plants contain a variety of active molecules with diverse pharmacological activities that can modulate disease pathogenesis by targeting many elements of the complex cellular pathway.[7] The anti-inflammatory and pain-relieving effects of these plant products are mediated by a variety of cellular mechanisms, including the inhibition of cytokines, adipokines, PGE2, NO, iNOS, lipid peroxidation, myeloperoxidase, COX-2, and MMPs, as well as the induction of antioxidant functions.[6] However, there have been few clinical studies on these traditional medicinal plants or their formulations.

Dr. Ortho Oil is a unique topical preparation of *Mentha piperita*, *Gaultheria fragrantissima, Linum usitatissimum*, *Vitex negundo*, *Cinnamomum camphora*, *Capsicum annuum*, *Pinus roxburghii*, *Celastrus paniculatus*, and *Sesamum indicum*. It is already being marketed in India for managing knee pain, lower back pain, joint stiffness, sports injury, and other joint inflammations. All these ingredients of Dr. Ortho oil are enlisted in the Ayurvedic text for their diverse health benefits. Recent pharmacological studies have shown the anti-inflammatory, analgesic and antioxidant potential of *Linum usitatissimum*,[8] *Cinnamomum camphora*,[9] *Mentha piperita*,[10] *Pinus roxburghii*,[11] *Gaultheria fragrantissima*,[12] *Vitex negundo*,[13] *Celastrus paniculatus*,[14] *Capsicum annuum*,[15] and *Sesamum indicum*.[16] Thus, the present study was to evaluate the efficacy and safety of Dr. Ortho pain relief oil in human volunteers with knee pain, lower back pain, joint stiffness, sports injury, and other joint inflammations.

MATERIALS AND METHODS

Trial Design

The current study was a non-randomised, open-label, single-arm post-marketing surveillance clinical trial. Considering the importance of pain management and the adverse effects of steroidal and NSAIDs used for pain management, we evaluated the efficacy and safety of "Dr. Ortho" topical pain relief formulation in healthy volunteers with various inflammatory conditions, including sports injury, knee pain, joint stiffness, lower back pain, neck rigidity, backache and other joint inflammations. The 30-day study duration consisted of a screening and baseline visit (visit 1, day 1), a final visit (Visit 2, day 30) and a telephonic follow-up (day 15±1). After receiving informed consent, subjects were evaluated for eligibility based on inclusion and exclusion criteria. After screening and baseline assessment at visit 1, the "Dr. Ortho" Oil was assigned to all subjects for 30 days. Subjects were instructed to apply 5 - 10 ml of the formulation on the affected area twice daily and gently massage. On day 15, a telephonic follow-up was made to monitor the subject's general well-being, concomitant medications and adverse effects. At the end of the study (Visit 2), the final assessment of the subjects was made.

Participants

Potential subjects were recruited through the outpatient orthopaedic department at Health India Hospital. No statistical consideration has been made for selecting the subject size. Based on the eligibility criteria, 125 subjects were recruited in this study voluntarily.

Inclusion and Exclusion Criteria

Patient inclusion criteria included male and female subjects aged between 18 -80 years who voluntarily signed a consent form after being sufficiently informed about the aim of this study; subjects with knee pain, joint pain and arthritis, acute sports injury, strains, sprain, chronic arthritis, back pain, knee pain and other joint pain; and an individual who was self-motivated and willing to participate in this study were included. Subjects who had undergone any surgery, or taken part in any clinical trial in the last 3 months, were pregnant and breastfeeding women. Subjects who refused to sign the informed consent form were excluded from the study.

Intervention

The "Dr. Ortho" is the oil-based polyherbal formulation of various Ayurvedic oils. *Linum usitatissimum* (flaxseed oil), *Cinnamomum camphora* (camphor oil), *Mentha piperita* (mint oil), *Pinus roxburghii* (Chir Oil), *Gaultheria fragrantissima* (wintergreen oil), *Vitex negundo* (nirgundi oil), *Celastrus paniculatus* (liquorice oil), *Capsicum annuum* (red pepper oil), and *Sesamum indicum* (sesame oil). The product is already marketed in India as a topical formulation for managing various inflammatory conditions, including acute sports injury, knee pain, inflammation in the joints, and reduction in muscle stiffness and lower back pain.

Outcome Measures

The study's primary endpoints were to assess the percentage of subjects with significant symptomatic reduction of joint muscle stiffness, neck rigidity, and backache using a pre-designed investigator assessment scale (IAS, 7 items) and subject's self-assessment questionaries (SSQ, 5 items). The secondary outcomes were improvement of symptom severity in the IAS scores and SSQ scores on VAS on the successive application compared to baseline. The symptoms severity scoring was made on a 4-point scale where 1 = no pain, 2 = mild pain, 3 = moderate pain and 4 = severe pain. The incidence of any AEs during the study.

Ethical Consideration

The study was carried out from Jul 2021- Oct 2021 at Health India Hospital (Bangalore, India) under strict compliance with the Declaration of Helsinki, ICMR ethical guidelines for biomedical research, and ICH guidelines for Good Clinical Practice (GCP). This study protocol was approved by the ACE Independent Ethics Committee (Protocol No: SBS/DIV/001/2021) and was prospectively registered with the Clinical Trials Registry - India (ID: CTRI/2021/07/034542) dated July 2, 2021. The study's purpose and procedure were explained to all the participants. A signed, dated, written informed consent was obtained from all patients before enrolment.

Statistical Analysis

Demographic and vital sign data were represented as means, percentages, ranges and standard deviations (SD). Where appropriate, baseline data were compared to the last visit using paired t-tests. Statistical analysis was performed using the SPSS statistical software (SPSS Inc., Chicago, USA). P values less than 0.05 are considered statistically significant.

RESULTS

Demographic and Baseline Data

One hundred twenty-five subjects were screened, 4 failed to meet the eligibility criteria, and 1 person withdrew consent. Hence, 120 subjects were selected to receive the treatment, of which 51.7% (62) were males and 48.3% (58) females, with a mean age of 48.34 ± 13.42 years. Due to the onset of an allergic reaction, one patient withdrew from the trial at the end of the second week.

Outcome Measures

Efficacy Outcomes: The primary endpoint of this study was a symptomatic decrease in various aspects of pain at the end of the treatment phase. Table 1 demonstrates the improvement in pain from baseline (Day 1) to the end of the study (Day 30). There was a significant reduction in all aspects of pain among the subjects on day 30 compared to day 1. The mean changes in SSQ and IAS scores at day 30 across different dimensions of pain were statistically significantly ($p<0.0001$) different compared to day 1 (Table 2). As shown in Table 2, the total SSQ score also decreased substantially from 9.12 ± 2.19 (Day 1) to 6.43 ± 1.59 (Day 30), with a mean difference of 2.69, CI 95% from 2.38 to 3.0, and $p<0.0001$. Similarly, the IAS total score also decreased from 13.37 ± 2.91 (Day 1) to 10.0 ± 1.49 (Day 30) [mean difference 3.37, 95% CI 0.04–3.70, and $p<0.0001$].

Safety

Dr. Ortho Oil was well tolerated by patients, with no participants reporting local or systemic adverse effects during the 30-day treatment period. Patients also reported no serious or systemic adverse effects.

Table 1: Change in outcome measures before and after the use of Dr. Ortho Oil

Questionaries	Baseline (Day 1), n = 120					End of the study (Day 30), n = 120			
	No no (%)	Mild no (%)	Moderate no (%)	Severe no (%)		No no (%)	Mild no (%)	Moderate no (%)	Severe no (%)
SSQ									
Pain during any activity	50 (41.67)	49 (40.83)	13 (10.83)	8 (6.67)		92 (76.67)	22 (18.3)	6 (5.0)	0 (0)
Pain restricts activities like walking and jogging	48 (40.0)	56 (46.67)	13 (10.83)	3 (2.50)		92 (76.67)	26 (21.67)	2 (1.67)	0 (0)
Pain while walking a short distance and inside the home	46 (38.33)	57 (47.50)	12 (10.0)	5 (4.17)		91 (75.83)	23 (19.17)	6 (5.0)	0 (0)
Pain in standing, not allowed to walk	38 (31.67)	56 (46.67)	19 (15.83)	7 (5.83)		93 (77.50)	18 (15.0)	7 (5.83)	2 (1.67)
Continuous pain; reduces sleep	41 (34.17)	55 (45.83)	22 (18.33)	2 (1.67)		91 (75.83)	26 (21.67)	3 (2.50)	0 (0)
IAS									
Pain during routine work	17 (14.17)	65 (54.17)	30 (25.0)	8 (6.67)		88 (73.33)	25 (20.83)	7 (5.83)	0 (0)
Pain during resting	46 (38.33)	48 (40.0)	22 (18.33)	4 (3.33)		98 (81.67)	16 (13.33)	6 (5.0)	0 (0)
Muscular pain	36 (30.0)	48 (40.0)	31 (25.83)	5 (4.17)		90 (75.0)	21 (17.50)	9 (7.50)	0 (0)
Swelling	53 (44.17)	52 (43.33)	13 (10.83)	2 (1.67)		96 (80.0)	19 (15.83)	5 (4.17)	0 (0)
Tenderness	47 (39.17)	59 (49.17)	13 (10.83)	0 (0)		95 (79.17)	21 (17.50)	4 (3.33)	0 (0)
Muscle stiffness	22 (18.3)	67 (55.83)	24 (20.0)	7 (5.83)		92 (76.67)	19 (15.83)	7 (5.83)	2 (1.67)
Mobility	49 (40.83)	53 (44.17)	18 (15.0)	0 (0)		94 (78.33)	21 (17.50)	5 (4.17)	0 (0)

Table 2: Mean change in SSQ and IAS severity scores of the patients on different dimensions of pain symptoms after the use of Dr. Ortho Oil

Questionaries	Baseline (day 1) (mean ± SD)	End of study (day 30) (mean ± SD)	Mean difference		CI 95%			p-value
					Lower	Upper		
SSQ								
Pain during any activity	1.86 ± 0.88	1.33 ± 0.61	0.53		0.39	0.66		< 0.0001
Pain restricts activities like walking and jogging	1.74 ± 0.75	1.23 ± 0.46	0.52		0.38	0.65		< 0.0001
Pain while walking a short distance and inside the home	1.75 ± 0.78	1.29 ± 0.56	0.46		0.29	0.63		< 0.0001
Pain in standing, not allowed to walk	1.93 ± 0.83	1.32 ± 0.58	0.62		0.48	0.76		< 0.0001
The continuous pain reduces sleep	1.83 ± 0.77	1.26 ± 0.49	0.56		0.43	0.72		< 0.0001
Total mean score	9.12 ± 2.19	6.43 ± 1.59	2.69		2.38	3.0		< 0.0001
IAS								
Pain during routine work	2.36 ± 0.74	1.65 ± 0.62	0.71		0.63	0.79		< 0.0001
Pain during resting	1.43 ± 0.55	1.12 ± 0.32	0.32		0.23	0.40		< 0.0001
Muscular pain	2.17 ± 0.67	1.78 ± 0.44	0.39		0.30	0.48		< 0.0001
Swelling	1.39 ± 0.55	1.03 ± 0.16	0.37		0.27	0.47		< 0.0001
Tenderness	1.94 ± 0.51	1.29 ± 0.46	0.65		0.56	0.74		< 0.0001
Muscle stiffness	2.53 ± 0.69	1.98 ± 0.35	0.55		0.46	0.64		< 0.0001
Mobility	1.55 ± 0.62	1.17 ± 0.37	0.38		0.29	0.47		< 0.0001
Total mean score	13.37 ± 2.91	10.0 ± 1.49	3.37		3.04	3.70		< 0.0001

DISCUSSION

In the modern system of medicine, various anti-inflammatory and analgesic drugs are available to treat pain and inflammation. These drugs are commonly associated with adverse effects with significant morbidity and mortality; hence, they can't be used as a treatment of choice for extended periods.[17] In this open-label, non-randomised study, we evaluated the efficacy of a Dr. Ortho polyherbal oil in reducing symptoms of sports injuries, knee and lower back pain, joint stiffness, neck stiffness, back pain, and joint inflammation. The efficacy results of Dr. Ortho Oil demonstrated a reduction in all dimensions of pain. It was also observed that SSQ and IAS scores were significantly ($p<0.0001$) reduced at the end of the study. No adverse or severe adverse events were observed after 30 days of application of Dr. Ortho Oil. Therefore, topical use of Dr. Ortho Oil was an effective, safe, and non-invasive modality to reduce pain and inflammation.

There were several clinical and preclinical studies on the effectiveness of each ingredient in Dr. Ortho Oil in reducing pain and inflammation. *Linum usitatissimum* oil inhibited different phases of acute inflammatory reactions by reducing leukocyte migration, vasodilatory (PGE3), and chemotactic (LTB5) eicosanoid production.[8] Another report suggested that *Linum usitatissimum* oil inhibited PGE2, leukotriene, histamine, bradykinin and arachidonic acid-induced inflammation. Particularly, inhibition of arachidonic acid-induced inflammation suggests its capacity to inhibit both COX and lipoxygenase (LOX) pathways of arachidonate metabolism.[18] *In vivo*, the essential oil of *Cinnamomum camphora* has been shown to suppress the expression of inflammatory mediators such as IL-1β, IL-6, and TNF-α in serum and tissue.[9] Authors also reported that the continuous application of *Cinnamomum camphora* essential oil reduced the levels of the serum pain-related mediators PGE2 and transient receptor potential melastatin-8 (TRPM8) in mice.[19] Menthol, a key ingredient in *Mentha piperita*, acts as an analgesic by stimulating and desensitising TRPM8 receptors in pain pathways.[20] *Mentha piperita* essential oil inhibited mice's production of NO, myeloperoxidase (MPO), IL-6, and TNF-α.[21] *Gaultheria fragrantissima* oil contains methyl salicylate, an anti-inflammatory and pain-relieving drug available over the counter. Methyl salicylate has been demonstrated to suppress NO, TNF-, IL-1, IL-6, and ROS.[22] *Vitex negundo* oil inhibited carrageenan-induced inflammation by selective inhibition of COX-2 receptors in rats.[13] *Celastrus paniculatus* seeds have been shown to have significant antinociceptive and anti-inflammatory action in

mice.[23] *Capsicum annuum* contains capsaicin as the main active ingredient, which has a wide range of pharmacological effects, including analgesic and anti-inflammatory activity.[24] Capsaicin treats pain by depleting substance P, defunctionalising and altering many pain-related processes.[25] *Sesamum indicum* oil and its active constituent, sesamin, showed significant antinociceptive and anti-inflammatory properties in animal and clinical studies.[26,27] *S. indicum* oil was found to inhibit monosodium urate monohydrate crystal-induced TNF-α, IL-1β, and IL-6 levels as well as activated mast cell counts, their NF-κB activity, and their IL-4 level.[26]

Dr. Ortho Oil has no definite mechanism for reducing pain and inflammation. However, from the different previous studies, several plausible mechanisms of action could be attributed to Dr. Ortho Oil's varying ingredients. The anti-inflammatory and analgesic activity of Dr. Ortho Oil seems to be hinged on a variety of mechanisms, such as inhibition of COX-2 receptors, TRPM8 receptor modulation, pro-inflammatory cytokine production, and defunctionalisation of other pathways involved in pain.

CONCLUSION

The study's findings showed that the topical use of Dr. Ortho Oil for 30 days reduced joint pain and improved joint function. This study suggests that Dr. Ortho Oil could be an alternative topical treatment modality for treating knee pain, low back pain, joint stiffness, sports injuries, and other joint inflammations.

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