

Evaluation of Anti-Arthritic Effect of Red Sandalwood and Curcumin Combination (Orthorev Oil)[®] on Topical Application in Rats

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ABSTRACT

Background: Arthritis, a common and debilitating condition characterized by joint inflammation, pain, and stiffness, affects millions of individuals worldwide. The standard treatment for arthritis is effective, but often comes with significant side effects and may not be suitable for long-term use. **Aim:** To evaluate the anti-arthritic effects of topical application of *Orthorev Oil*[®] containing a combination of red sandalwood and curcumin in a rat model of arthritis. **Materials and Methods:** Wistar rats weighing 200-250 g were included in the study. Ethical Approval obtained from the institutional animal ethics committee. Baseline Measurements readings taken for paw volume using a plethysmometer. Arthritis induced with in Complete Freund's Adjuvant 0.1 mL injected into the plantar surface of the left hind paw of each rat. The rats observed for signs of arthritis development, typically characterized by paw swelling and redness, within few days. Treatments as per the groups given topically to each rat once daily for 21 days. The rats in the vehicle control group received the ointment base without active ingredients. The paw volume measured on days 0, 7, 14, and 21. **Results:** Significant increase in paw volume in comparison with control indicated the development of arthritis. Topical application significantly decreased paw volume in drug treated groups along with reduction in inflammatory markers. **Conclusion:** The topical application of *Orthorev Oil*[®] containing Red Sandalwood and Curcumin demonstrated significant anti-arthritic effects in a rat model of paw oedema along with reduction in inflammatory markers-TNF- α , IL-6, and CRP.

Keywords: Topical, Rheumatoid arthritis, Paw volume, Red sandalwood, Curcumin.

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INTRODUCTION

Arthritis, a common and debilitating condition characterized by joint inflammation, pain, and stiffness, affects millions of individuals worldwide.¹ Among its various forms, Rheumatoid Arthritis (RA) is particularly severe, leading to significant morbidity and reduced quality of life.² The standard treatment for arthritis includes Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, and Disease-Modifying Antirheumatic Drugs (DMARDs).³ While these therapies can be effective, they often come with significant side effects and may not be suitable for long-term use. Thus, there is a growing interest in exploring alternative and complementary therapies that offer efficacy with fewer adverse effects.⁴

Red sandalwood (*Pterocarpus santalinus*) and curcumin (the active component of turmeric, *Curcuma longa*) are two natural compounds with well-documented anti-inflammatory and antioxidant properties.^{5,6} Red sandalwood has been traditionally used in Ayurvedic medicine for its wound healing and anti-inflammatory effects, while curcumin is widely recognized for its ability to modulate inflammatory pathways and reduce oxidative stress. Both compounds have shown promise in preclinical studies for their potential to alleviate symptoms of arthritis.^{7,8}

Combining red sandalwood and curcumin in a topical formulation adds the benefits of both agents, potentially offering a synergistic effect in managing arthritis. Topical applications provide the advantage of localized treatment with minimal systemic absorption, reducing the risk of systemic side effects. This approach is particularly appealing for chronic conditions like arthritis, where long-term management is necessary.⁹

This study aims to evaluate the anti-arthritic effects of a topical application containing a combination of red sandalwood and curcumin (*Orthorev Oil*[®]) in a rat model of arthritis induced by Complete Freund's Adjuvant (CFA). By assessing parameters



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such as paw edema, pain response, and biochemical parameters, the study seeks to determine the efficacy of this combination treatment in reducing inflammation and improving joint function. Present study was undertaken to get valuable insights into the potential of red sandalwood and curcumin as a complementary therapy for arthritis and evidence for further clinical research and application.

MATERIALS AND METHODS

Ethical Approval was obtained for animal experimentation from the Institutional Animal Ethics Committee (IAEC)-BVDUMC/2217/2024/2/20. Total 32 wistar rats, of either sex, weighing 150-200 g obtained from Central Animal House, Bharati Vidyapeeth Medical College, Pune wistar rats were included in the study. Housing was done as 4 rats per cage in polypropylene cages with autoclaved rice husk as bedding material. 10% air exhausts in the air conditioning unit, relative humidity of 60%, temperature 25°C and 14 hr light and 10 hr dark cycle was maintained. Laboratory rat diet (pellets) were given to the rats obtained from Nutrivet Life sciences, Pune (An ISO 9001: 2015 Certified Company) as 60 g / 4 animals / day in the morning at 10 am and were kept constant throughout the study. Purified aqua guard water was provided *ad libitum*. All laboratory procedures were performed in accordance to CCSEA guidelines.

Dosing was done once /day in the morning for 21 days as a topical application.

Test material red sandalwood and curcumin combination (Orthorev Oil)® was provided by the sponsor which is combination of oils such as Mahanarayan oil 40% w/v, Gandhpura tail 7.9%, Kapoor (*Cinnamomum camphora*) 4% w/v, Turpin oil (Turpentine) 3%w/v, Red pepper oil 5 0.1%, Sat peppermint 1%, Curcumin 3%, Red sandalwood 5%, Guggal oil (*Commiphora wightii*) 5% w/v, Panchguna oil 5%, Pudina Satwa (*Mentha arvensis*) 1%, Mahavishgarbha oil 10%, Til oil (*Seasamum indicum*) and optionally along with pharmaceutically acceptable excipients.

Baseline measurements were taken for initial body weight of each rat. The baseline paw volume was measured using plethysmometer. Arthritis was induced with CFA 0.1 mL injection into the plantar surface of the left hind paw of each rat. The rats were observed for signs of arthritis development, typically characterized by paw swelling and redness, within a few days.

Groups- Rats were randomized as per the weight and sex maintaining the uniformity in four experimental groups ($n=8$ per group):

Group I: Control (vehicle treatment), Group II: Disease control (vehicle treatment).

Group III: Orthorev Oil ® & Group IV: Diclofenac gel.

Marking on the foot was done and respective treatments were applied topically to the arthritic paw, upto the marking, of each rat once daily for 21 days. The rats in the vehicle control group received the ointment base without active ingredients. The paw volume of each rat was measured using a plethysmometer on days 0, 7, 14, and 21. The percentage inhibition of paw edema for each treatment group was measured.

At the end of the treatment period, blood was withdrawn from the retro-orbital plexus under ketamine anaesthesia and sent for biochemical analysis.

Statistical Analysis- Statistical analysis (e.g., t-tests, ANOVA) was performed to compare the anti-arthritis efficacy of the red sandalwood and curcumin combination oil with the control and standard treatments. The data presented as Mean±Standard Deviation (SD) and the p -values (<0.05) was considered as statistical significant.

RESULTS

Paw volume was significantly increased ($p<0.001$) in all the groups after the injection of CFA at the baseline in comparison with the control group. Increase in the paw volume remained same throughout the study period in the disease control group. In Orthorev oil group, the oedema started reducing from the day of oil application and significant reduction ($p<0.001$) was seen from day 14 to day 21. Similar findings were seen in diclofenac gel treated group.

TNF α levels were significantly increased ($p<0.05$) in disease control group showing the inflammation. Reduction in the TNF α levels was seen in the drug treated groups but it was statistically non-significant.

IL6 levels were significantly increased ($p<0.01$) in disease control group depicting inflammation. Reduction in the IL6 levels was seen in the drug treated groups but it was statistically non-significant.

CRP levels were significantly raised ($p<0.05$) in disease control group due to inflammation. Reduction in the CRP levels was seen in the drug treated groups but it was statistically non-significant.

DISCUSSION

Arthritis remains a significant global health issue, with a growing prevalence due to aging populations, sedentary lifestyles, and increasing rates of obesity. The most common being Osteoarthritis (OA) and Rheumatoid Arthritis (RA)¹⁰ affecting the quality of life.¹¹ The treatment for arthritis has significantly expanded with the recent advances, particularly with the biologic therapies, JAK inhibitors, and targeted immune modulators. These drugs are revolutionizing the management of autoimmune forms of arthritis, offering improved outcomes for many patients. However, challenges remain, such as side effects, cost, and accessibility.^{12,13}

Complete Freund's Adjuvant (CFA) induced arthritis is a reliable animal model for inducing experimental arthritis,¹⁴ which allows to study the immunological mechanisms of Rheumatoid Arthritis (RA) and evaluate potential treatments. This model is widely used, and essential for the development and testing of new therapies for autoimmune diseases like rheumatoid arthritis.

Topical agents play an important role in the management of arthritis, especially for localized pain and inflammation.¹⁵ These treatments are applied directly to the skin over the affected joints, offering a more targeted approach to pain relief with fewer systemic side effects compared to oral medications. Topical therapies are commonly used as part of a comprehensive treatment plan, often alongside oral medications, physical therapy, and lifestyle changes.

There are total eleven oils are used as an adjuvant in the preparation of which Wintergreen oil (*Gaultheria procumbens*), Mahanarayan oil,¹⁶ Camphoris,¹⁷ Guggal oil (*Commiphora wightii*),¹⁸ Mahamash oil,¹⁹ Panchguna oil, Pudina Satva and Til oil (*Seasamum indicum*). The eucalyptus and peppermint oils were used as a top note. The rosemary, sweet marjoram, lavender, and ginger oils were used as a 10-middle note. The patchouli oil was used as a base note.

Red Sandalwood and Curcumin are known for their individual anti-inflammatory properties.²⁰ Red Sandalwood (*Pterocarpus santalinus*) has been historically used in traditional medicine for its antioxidant and anti-inflammatory effects. Previous studies suggest that its active compounds may inhibit pro-inflammatory

cytokines and modulate immune responses, contributing to its anti-arthritis effects.²¹ Curcumin, the active compound in turmeric, is well-documented for its potent anti-inflammatory, antioxidant, and analgesic properties. Curcumin exerts its therapeutic effects by modulating key signaling pathways involved in inflammation, such as NF- κ B, COX-2, and TNF- α , which are central to the pathogenesis of arthritis.²²

In combination, these two agents may act synergistically, enhancing each other's effects. The topical application of Orthorev Oil® likely allowed for localized delivery of these active compounds, potentially leading to higher concentrations at the site of inflammation in the paw. This could explain the significant reduction in paw oedema observed in the Orthorev Oil® treated rats (Table 1), as the active ingredients in the oil may directly target inflammatory mediators in the affected tissues. Moreover, the absorption of Orthorev Oil® through the skin may facilitate the direct interaction of the active compounds with local inflammatory cells and tissues, leading to faster and more targeted relief, which may be subject to systemic metabolic degradation.

TNF- α and IL-6 are central pro-inflammatory cytokines that play pivotal roles in the pathogenesis of arthritis.²³ TNF- α is a key mediator that promotes the activation of various downstream inflammatory pathways, including the production of other cytokines and enzymes that contribute to joint inflammation, cartilage degradation, and bone resorption. IL-6, similarly, is involved in the acute-phase response, and its elevated levels are often correlated with the severity of inflammatory conditions such as rheumatoid arthritis.²⁴

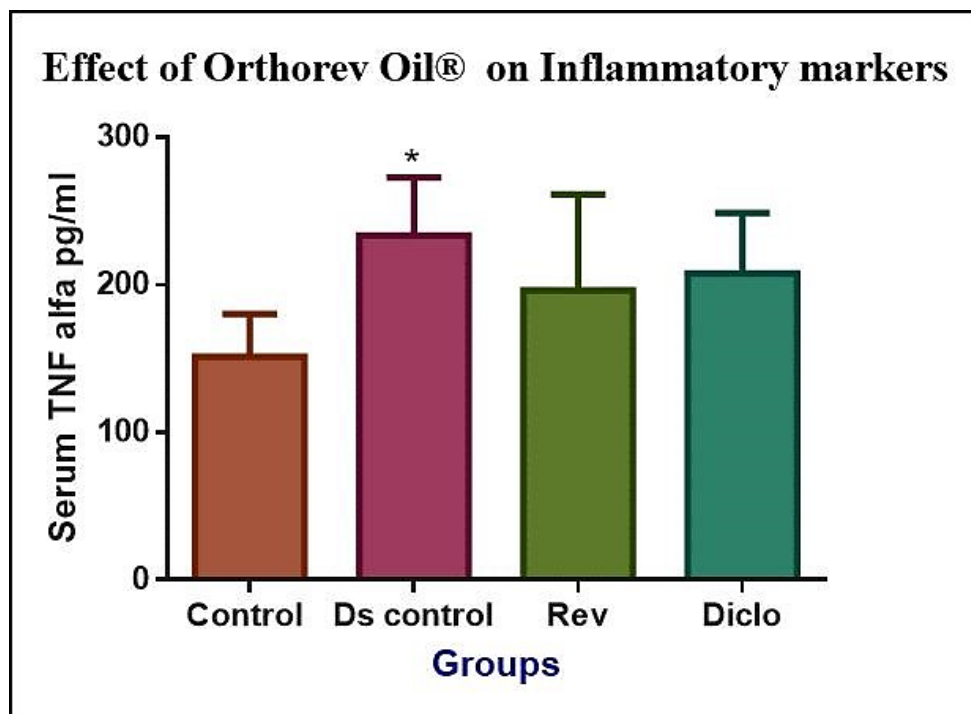


Figure 1: Effect of *Orthorev oil* on TNF α in CFA induced arthritis in rats. Values are expressed as Mean \pm SD; n=6; One way ANOVA followed by Tukey's test, * $p < 0.05$ in comparison with control group.

In this study, treatment with Orthorev Oil® resulted in a significant reduction in both TNF- α (Figure 1) and IL-6 levels (Figure 2) in the paw tissue of treated rats compared to the untreated disease control group. This suggests that the combination of Red Sandalwood and Curcumin in the oil formulation may have a direct effect on modulating the inflammatory cytokine network. Previous studies have highlighted the ability of Curcumin to inhibit the NF- κ B pathway, a critical signaling cascade that regulates the expression of TNF- α and IL-6, thereby reducing their production.²⁵ Similarly, Red Sandalwood has demonstrated anti-inflammatory effects in traditional medicine, likely due to its ability to modulate immune responses and decrease the secretion of inflammatory mediators.

C-Reactive Protein (CRP) is a key marker of systemic inflammation, elevated CRP levels are commonly seen in patients with inflammatory diseases, including rheumatoid arthritis, and are associated with increased disease activity and severity.²⁶ Treatment with Orthorev Oil® was associated with a significant reduction in CRP levels (Figure 3) in the treated rats, indicating a systemic reduction in inflammation. The reduction in TNF- α ,

IL-6, and CRP observed in this study suggests that Orthorev Oil® may be an effective treatment option for managing inflammatory arthritis.

Conventional anti-arthritic treatments, such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)²⁷ and Disease-Modifying Antirheumatic Drugs (DMARDs),²⁸ often have significant side effects, particularly when used long-term. These can include gastrointestinal issues, renal dysfunction, and cardiovascular complications. In contrast, the topical nature of Orthorev Oil® offers the advantage of localized treatment with minimal systemic exposure.

By reducing TNF- α and IL-6 levels, Orthorev Oil® may help to suppress the inflammatory cascade in the affected tissues, leading to a reduction in oedema and an improvement in the overall clinical symptoms of arthritis, such as pain and joint swelling. The study's results provide a comprehensive insight into the therapeutic potential of Orthorev Oil® when topically applied, showcasing its ability to modulate the inflammatory processes associated with arthritis.

Table 1: Effect of Orthorev oil® on CFA induced Paw oedema in rats.

Groups	Baseline	Day 7	Day 14	Day 21
Control	2.25±0.16	2.19±0.35	2.20±0.09	2.06±0.04
Disease Control	2.93±0.30 ^{sss}	2.92±0.25 ^{sss}	2.84±0.19 ^{sss}	2.82±0.21 ^{sss}
Orthorev oil	2.88±0.39 ^{sss}	2.75±0.31	2.33±0.37 ^{***}	1.87±0.29 ^{***}
Diclofenac	2.76±0.20 ^{sss}	2.63±0.34	2.03±0.44 ^{***}	1.82±0.33 ^{***}

Values are expressed as Mean±SD; n=8; One-way ANOVA followed by Tukey's test ^{sss}p<0.001 in comparison with control group *p<0.05, **p<0.01 & ***p<0.001 in comparison with disease control group.

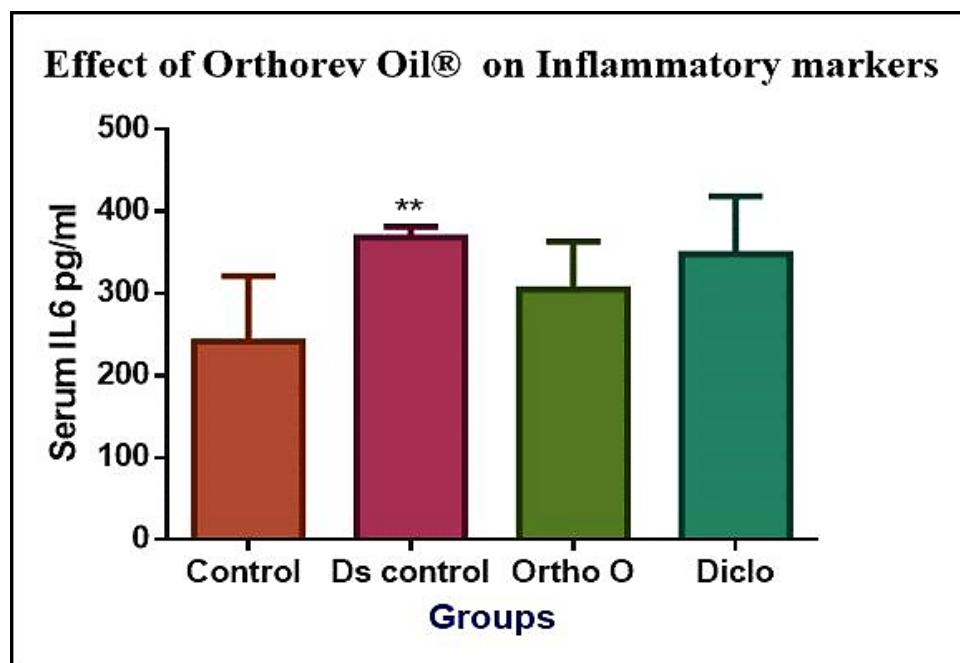


Figure 2: Effect of Orthorev oil® on IL6 in CFA induced arthritis in rats. Values are expressed as Mean±SD; n=6; One way ANOVA followed by Tukey's test, **p<0.01 in comparison with control group.

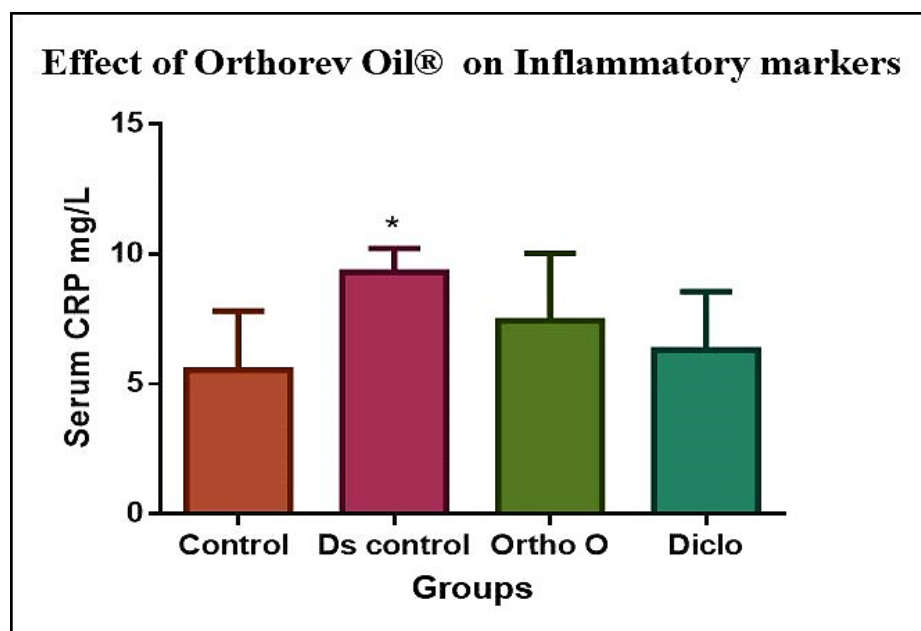


Figure 3: Effect of *Orthorev oil*® on CRP in CFA induced arthritis in rats. Values are expressed as Mean±SD; n=6; One way ANOVA followed by Tukey's test, * $p < 0.05$ in comparison with control group.

CONCLUSION

In conclusion, the topical application of Orthorev Oil® containing Red Sandalwood and Curcumin demonstrated significant anti-arthritic effects in a rat model of paw oedema, primarily through the reduction of paw oedema. Even if the reduction in inflammatory markers such as TNF- α , IL-6, and CRP was statistically non-significant, there was some suppression observed in these markers. The combination of these two natural ingredients along with the different oils appears to have a synergistic effect, providing a promising alternative to conventional anti-arthritic treatments.

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ABBREVIATIONS

CFA: Complete Freund's Adjuvant; **CRP:** C Reactive Protein; **TNF α :** Tumor Necrosis Factor α ; **IL6:** Interleukin 6; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **DMARDs:** Disease Modifying Anti-Rheumatoid Drugs; **NF- κ B:** Nuclear Factor κ B; **COX-2:** Cyclo-Oxygenase 2; **RA:** Rheumatoid Arthritis; **OA:** Osteoarthritis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUMMARY

Effectiveness of Orthorev Oil®, a topical treatment made with red sandalwood and curcumin, was evaluated for treatment of arthritis in rats. Arthritis was induced in wistar rats by injecting Complete Freund's Adjuvant into their hind paws. After confirming inflammation through swelling, oil was applied daily for 21 days. Rats treated with Orthorev Oil® showed a clear reduction in paw swelling compared to the control group, which only received the ointment base without the active ingredients. In addition to reducing the physical symptoms of arthritis, the treatment also lowered key inflammatory markers like TNF- α , IL-6, and CRP. Overall, the oil demonstrated promising anti-arthritic effects and may offer a safer alternative for managing arthritis symptoms topically.

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