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International Journal of Complementary & Alternative Medicine

Research Article

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A pilot clinical study to manifest the efficacy of Pankajakasthuri orthoherb cream/thermagel in the treatment of patients diagnosed with osteoarthritis

Abstract

Osteoarthritis (OA) is a major form of arthritis associated with severe joint pain that reduces the quality of life. Various pharmacological interventions may be utilized for arthritis treatment when non-pharmacological therapy is insufficient. However, pharmacological treatment can have serious side effects and high costs. Therefore, alternative therapies have been under investigation to manage this condition. Medicinal plants and their secondary metabolites are significant as alternative treatments available for inflammatory diseases. In the current study, we investigated the efficacy of Pankajakasthuri orthoherb cream/thermagel in managing OA. A total of thirty patients over 18 years of age diagnosed with osteoarthritis were enrolled from July 1st, 2021 to August 31st, 2021 for the clinical trial. All subjects were applied with Pankajakasthuri Orthoherb cream/thermagel 1gm (pea size) at a time, externally, thrice daily with an interval of 6 hours. The following clinical parameters, viz. pain, swelling, stiffness, tenderness, pain on movement, were used for evaluating the effect of Pankajakasthuri Orthoherb cream/thermagel in managing osteoarthritis conditions. The intervention was continued for one month and assessments were done before treatment and on the 10th, 20th and 30th days after treatment. The study results showed that Pankajakasthuri orthoherb cream/thermagel recorded significant improvement in the clinical condition associated with osteoarthritis within 30 days of intervention when analyzed using t-test. This clinical study proved that Pankajakasthuri orthoherb cream/thermagel is highly effective in managing the clinical conditions associated with osteoarthritis.

Keywords: anti-inflammatory, analgesic, polyherbal cream, thermagel, topical application, pain

Volume 15 Issue 1 - 2022

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Received: December 18, 2021 | **Published:** February 08, 2022

Introduction

Arthritis is a common health issue that affects millions of people worldwide.[1] Patients suffering from arthritis struggle with severe joint pain and nearly half of all adults with arthritis experience persistent pain.[1] The most common type of arthritis is osteoarthritis (OA), also known as degenerative joint disease.[2] OA is a biomechanical and inflammatory disease influenced by several factors such as mechanical stress, oxidative stress, injury, etc.[3] OA is characterized by joint cartilage degeneration, changes in the underlying bone, and synovitis.[3] In addition to this, extracellular matrix breakdown can trigger the accumulation of innate immune cells that lead to inflammation and tissue destruction.[3] OA has a slow onset, often beginning later in life and leading to severe disability for the affected person. Symptoms of OA include localized joint pain and tenderness as well as stiffness in the morning and after periods of activity.[1]

Pain and inflammation are the most common and main symptoms of many diseases, especially in the case of arthritic conditions. Inflammation is an adaptive response involving multiple defence cell types and soluble mediators that is triggered in response to noxious stimuli and is responsible for eliminating infectious agents and regulating tissue homeostasis.[4–6] These activated defense cells produce and release a variety of inflammatory mediators, including cytokines like interleukin (IL-1) and tumour necrosis factor (TNF-α).[7,8] The pain, redness, and swelling characterize the inflammation process.[9] Many studies have indicated that inflammatory reactions are implicated in the progression of several disorders, such as aging, rheumatoid arthritis, skin inflammation, and cardiovascular dysfunction.[10]

India has a high prevalence of arthritis, which is a chronic inflammatory condition affecting about 15% of the population, i.e. over 180million people affected by it.[11] It is associated with joint inflammation with immune cell infiltration, pain, swelling and synovial hyperplasia. Chronic inflammation leads to joint deformity and compromises the activities of daily living. The treatment agents used for chronic inflammatory conditions include non-steroidal inflammatory drugs and glucocorticosteroids which are associated with serious adverse effects on prolonged use and unsatisfactory response.[11]

Nowadays, the drugs used for skin inflammation treatment are corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).[12] However, the routine treatment of inflammatory diseases with these agents over long periods of time leads to adverse effects, including pruritus, irritations, skin dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, skin maceration, stretch marks and miliary.[12,14] The adverse effects justify the search for new healings from medicinal plants, which usually present less toxic effects.[14]

Anti-inflammatory and pain medications, particularly those used for a long duration of time to manage chronic inflammation/pain conditions; can have serious and potentially life-threatening adverse effects. As patients' age and their lists of comorbid disease states grow, medication management becomes increasingly more complex and options for pharmacological interventions diminish. For this reason, a topically applied and localized drug effect may be favorable. Topicals are growing in preference given their localized drug delivery and low systemic absorption.[15] Both aspects result in a more favorable

side effect profile for patients seeking pain relief. Topical medications differ from transdermal medications in that transdermal drug delivery systems are designed to deliver drugs systemically through cutaneous absorption from external application.[15] Topical preparations are designed for localized effects, thereby minimizing systemic effects.

Keeping these points, recently Pankajakasthuri Herbals India Pvt. Ltd. has formulated Pankajakasthuri orthoherb cream/thermagel (DL. NO: 50/25D/96) for managing the severe inflammation and joint pain. This product contains 23 active Ayurvedic herbal ingredients like *Adathoda vasica, Aegle marmelos, Ricinus communis, Azadirachta indica, Sida retusa, Tragia involucrata,* etc., along with essential oils that could increase blood circulation/blood pooling through vasodilation and could relieve pain through counter stimulation. Several research articles were available on the anti-inflammatory and analgesic properties of the ingredients used for the formulation of Pankajakasthuri orthoherb cream/thermagel.[16-25] Furthermore, this formulation recorded significant antiinflammatory and analgesic effects in the preclinical studies.[26] A toxicity probe also revealed that this formulation is safe and free from any toxic effects.[27]

Still, advanced clinical studies are needed to introduce Pankajakasthuri orthoherb cream/thermagel to the market for its widespread clinical application. Hence, the present pilot clinical study was intended to carry out the anti-inflammatory and analgesic activities of orthoherb cream/thermagel in patients presenting with osteoarthritis conditions.

Materials and methods

Test drug (Pankajakasthuri orthoherb cream/ thermagel)

The test drug is Pankajakasthuri orthoherb cream/thermagel, an herbal-based cream/thermagel preparation for topical administration. Pankajakasthuri orthoherb cream/thermagel is manufactured at Good Manufacturing Practices approved production line at Pankajakasthuri Herbals India Pvt. Ltd. situated at Poovachal, Kattakada, Thiruvananthapuram, Kerala, India. The ingredients used for the formulation of Pankajakasthuri orthoherb cream/thermagel is provided in Table 1.

Table 1 Ingredient used for the formulation of Pankajakasthuri orthoherb cream/thermagel in managing

S. No	Sanskrit name	Scientific name
1	Vasa	*Adhatoda vasica*
2	Maricham	*Piper nigrum*
3	Thwak	*Cinnamomum cassia*
4	Bilwa	*Aegle marmelos*
5	Eranda	*Ricinus communis*
6	Lavanga	*Syzygium aromaticum*
7	Guggulu	*Commiphora wightii*
8	Jati	*Jasminum grandiflorum*
9	Pashanabheda	*Curculiginis orchioides*
10	Amalaki	*Embelica officinalis*
11	Gokshuram	*Tribulus terrestris*
12	Pata	*Cyclea peltata*
13	Satavari	*Asparagus racemosus*
14	Kataka	*Strychnos potatorum*
15	Nimba	*Azadirachta indica*
16	Nirgundi	*Vitex negundo*
17	Chitraka	*Plumbago zeylanica*
18	Bala	*Sida cordifolia*
19	Manjista	*Rubia cordifolia*
20	Punarnava	*Boerhavia diffusa*
21	Gunja	*Abrus precatorius*
22	Dusparsa	*Tragia involucrate*
23	Sahachara	*Barleria prionitis*

Study site

The study was conducted among patients who attended the OPD of Pankajakasthuri Ayurveda Medical College Hospital & PG Centre, Killy, Kattakada, Thiruvananthapuram, Kerala, India.

Study design

A single-group pre-test and post-test clinical trial with a sample size of 30 patients with osteoarthritis was used in the study. This study was cleared by the IEC with a vide approval number (PKAMC/IEC/PS/01/2021) and was carried out as per the International Conference of Harmonization Good Clinical Practices Guidelines (ICH-GCP). The trials were conducted between 01st July and 31st August 2021.

Types of participants

Participants (18years or older) who were diagnosed with knee OA based on radiographic evidence and clinical criteria.

Inclusion criteria

a) Subjects of either gender from an age group between 18 to 70years, having symptoms of OA for minimum 6 months and maximum 5years.

b) Classical signs and symptoms of OA – Pain during movement and weight bearing, Swelling, Stiffness. Also fulfilling the classical criteria of Osteoarthritis of knee joints mentioned in Ayurvedic texts viz. Shoola (pain), Akunchanaprasarana vedana (pain on flexion and extension), Shotha (oedema) and Sthambha (stiffness of the joints).

c) Diagnosed case of OA Knee based on Kellegren-Lawerence grading scale (Grade-1 &2)

d) Subjects willing to sign the informed consent form.

Exclusion criteria

The following are the exclusion criteria of the study:

a) Secondary arthritic conditions, Fractures, Ligament tear, Dislocation, Osteomyelitis, SLE, Tumors Bone density disorders.

b) Anatomical joint deformities, NSAID/Analgesic/steroid treatment for Osteoarthritis.

c) Patients who have undergone major surgery in the affected joint.

d) Patients with known skin hypersensitivity.

e) Subjects not willing to sign the informed consent form.

Intervention

All study subjects were applied with Pankajakasthuri orthoherb cream/thermagel for approx. 1 gm (Pea size) at a time, externally thrice daily with an interval of 6 hours. The intervention was continued for one month and assessments were done before treatment, on the 10th, 20th and 30th after treatment.

Assessment criteria

The assessment of the improvement of the clinical condition in the patient was done mainly on the basis of relief from the signs and symptoms of the disease. To assess the effect of therapy objectively, all the signs and symptoms were given a score depending upon their severity. The assessment was based on grading the symptoms like Pain, Swelling in joints, Stiffness, Tenderness and Pain on movement.

Observation period

The above five assessment criteria were observed before treatment, 10th, 20th and 30th after treatment.

Statistical analysis

All the results were expressed as mean ± SEM. Data analysis was performed using SPSS version 20.0 and Microsoft Office Excel 2007. Statistical significance set at *P*, 0.05.

Results

This pilot study includes 30 patients to study the efficacy of Pankajakasthuri orthoherb cream/thermagel in patients suffering from osteoarthritis. The observations procured on the assessment parameters of 30 patients before treatment and 10th, 20th and 30th day after treatment were statistically analyzed to determine the effect of the treatment of osteoarthritis with a polyherbal formulation – Pankajakasthuri orthoherb cream/thermagel.

Effect of treatment on pain

The mean score of the criteria pain before treatment was 3.433±0.114, which reduced to 2.466±0.124 on the 10th day after the treatment, which further reduced to 1.433±0.092 on 20th day after treatment and 0.1±0.005 on the 30th day after treatment. As the p-value of the paired t-test was found to be <0.0001, it can be inferred that pain decreased significantly from before treatment to the 10th, 20th and 30th day after treatment (Figure 1).

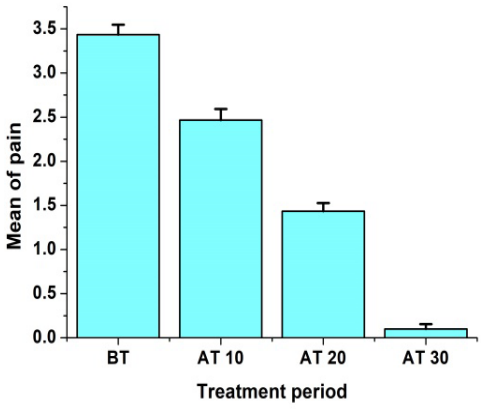

Figure 1 Effect of Pankajakasthuri orthoherb cream/thermagel on pain.

Effect of treatment on swelling

The mean score of the criteria swelling for the treatment was 2.466±0.133, which reduced to 1.566±0.156 on the 10th day after the treatment, which further reduced to 0.566±0.092 on the 20th day after treatment and 0.366±0.089 on the 30th day after treatment. As the p-value of the paired t-test is found to be <0.0001, it can be inferred that swelling decreased significantly from before treatment to the 10th, 20th and 30th days after treatment (Figure 2).

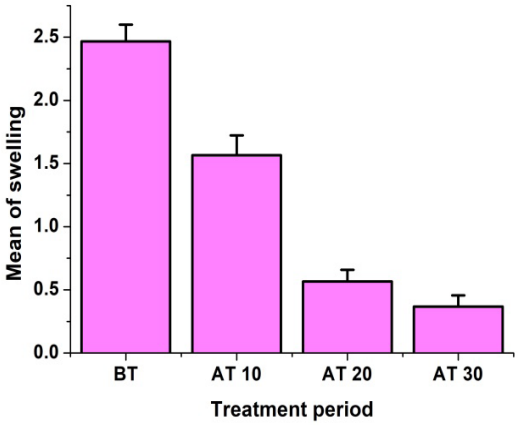

Figure 2 Effect of Pankajakasthuri orthoherb cream/thermagel on swelling.

Effect of treatment on stiffness

The mean score of the criteria for stiffness before treatment was 3.233±0.149, which reduced to 2.233±0.114 on the 10th day after the treatment, which further reduced to 1.333±0.087 on the 20th day after treatment and 0.6±0.090 on the 30th day after treatment. As the p-value of the paired t-test is found to be <0.0001, it can be inferred that stiffness decreased significantly from before treatment to the 10th, 20th and 30th days after treatment (Figure 3).

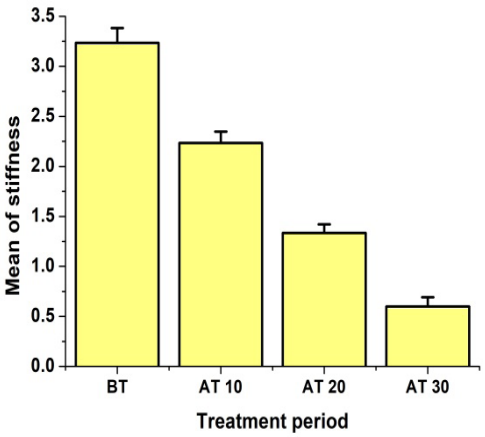

Figure 3 Effect of Pankajakasthuri orthoherb cream/thermagel on stiffness.

Effect of treatment on tenderness

The mean score of the criteria for tenderness before treatment was 2.633±0.089, which reduced to 1.500±0.092 on the 10th day after the treatment, which further reduced to 1.066±0.046 on the 20th day after treatment and 0.466±0.092 on 30th day after treatment. As the p- value of the paired t-test is found to be <0.0001, it can be inferred that tenderness decreased significantly from before treatment to the 10th, 20th and 30th days after treatment (Figure 4).

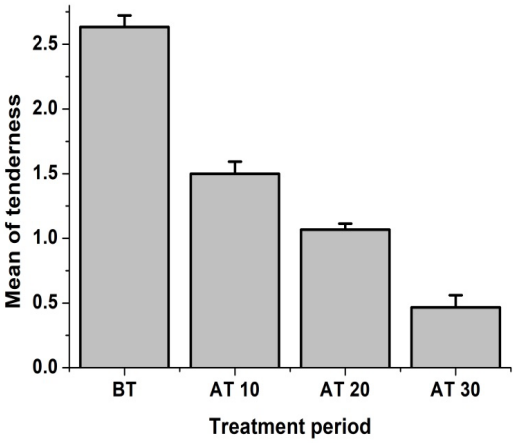

Figure 4 Effect of Pankajakasthuri orthoherb cream/thermagel on tenderness.

Effect of treatment in pain on movement

The mean score of the criteria for pain on movement before treatment was 3.366±0.147, which reduced to 2.400±0.113 on the 10th day after the treatment, which further reduced to 1.300±0.466 on the 20th day after treatment, and 0.333±0.479 on the 30th day after treatment. As the p-value of the paired t-test is found to be <0.0001, it can be inferred that pain on movement decreased significantly from before treatment to the 10th, 20th and 30th days after treatment (Figure 5).

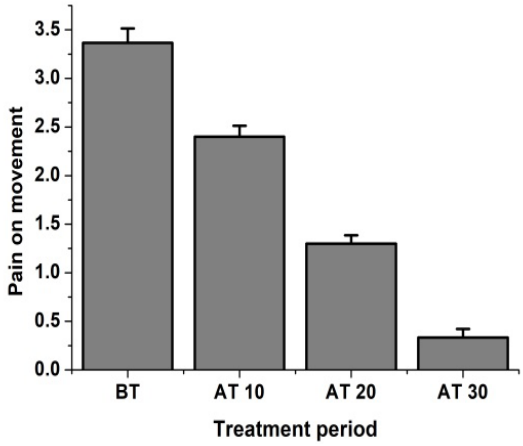

Figure 5 Effect of Pankajakasthuri orthoherb cream/thermagel on pain while moving.

Discussion

Diseases affecting the musculoskeletal system are a major cause of disability worldwide, especially in the elderly population. OA is the most common musculoskeletal disorder that causes a significant financial burden on healthcare systems. This disease is accompanied by a number of symptoms, with pain being the most important one. Joint pain caused by OA reduces the patient's quality of life and causes remarkable morbidity for patients. In addition to these agents, various types of oral neuromodulators, such as certain antidepressants and anticonvulsants, are often prescribed for chronic pain. Although potentially effective in providing meaningful pain relief, oral administration of these systemic agents frequently results in adverse events (AEs), which may preclude their ongoing use and result in discontinuation. However, unfortunately, most of the drugs currently available on the market are not very effective in OA patients and can only cause small or at their best, modest relief of symptoms. Because of the relatively low effects of common drugs used for treating OA and their adverse effects that can cause significant morbidity and mortality, especially for elderly patients, researchers around the globe are looking for safer and more effective therapies for OA. A challenge in osteoarthritis treatment is deciding which medications will provide the greatest symptom relief with the lowest serious adverse effects. Meanwhile, people who make use of complementary and alternative medicine believe that using "natural" treatments is safer than conventional medical treatments.[28] Thus, topical analgesics were developed, in part, to provide the symptomatic benefits seen with oral agents but without the systemic AEs associated with oral analgesics. Topical administration of analgesics can produce clinically effective drug concentrations at a peripherally located site of injury or inflammation, without resulting in high systemic concentrations that may increase the likelihood of AEs.[29-32] The present study attempted to determine the efficacy of Pankajakasthuri orthoherb cream/thermagel in the management of osteoarthritis by assessing prescribed parameters. This study revealed many positive and promising results that fulfil the study objectives.

Commiphora wightii (Guggulu) one of the major ingredients in our formulation, possesses anti-inflammatory and analgesic actions. It helps in the prevention of degenerative changes that may occur in bones and joints due to arthritis. *C. wightii* reduces inflammation, stiffness, and pain associated with arthritis while also improving joint mobility.[33] Earlier pharmacological studies on *C. wightii* have established its anti-inflammatory and anti-arthritic activities in formaldehyde-induced arthritis, in albino rats.[34] A significant anti-inflammatory and anti-arthritic activity of oleo-gum resin has been reported against carrageenan-induced rat paw edema, granuloma pouch, as well as adjuvant arthritis.[35] A study presented at a recent meeting of the American College of Rheumatology, has shown that herbal Ayurvedic therapy consists of *C. wightii*, which is as effective in treating knee osteoarthritis as a commonly prescribed medication (Celebrex) and Glucosamine, and with fewer side effects. In addition, *C. wightii* has been shown to be a potent inhibitor of the enzyme, Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NFKB), which regulates the body's inflammatory response. There are several studies that show how inflammation and joint swelling are decreased after administration of the extracts of *C. wightii* resin.[36]

Vitex nigundo (Nirgundi) possesses both analgesic and anti-inflammatory actions.[37] It has been used to treat disorders characterised by swelling and pain in the majority of the ayurvedic text books.[38,39] It has been shown to have a preventive effect on the development of formaldehyde-induced experimental arthritis.[40] The present study supports these earlier observations and recommendations by the classical reference dictionaries of ayurveda. The traditional use of *V. negundo* seeds as an anti-inflammatory agent, together with modern pharmacological studies, suggested it has potential therapeutic effects in the treatment of RA.

Aegle marmelos (L.) Correa commonly known as Beal or Bilwa belongs to the family Rutaceae and has been widely used in Ayurveda for the treatment of *Sandhigata vata*. In vitro anti- arthritic activity of different extracts of *A. marmelos* was screened against protein denaturation against bovine serum albumin and egg albumin. The fruit extract of *A. marmelos* showed significantly higher anti-arthritic activity at increasing concentration. The flavonoids and triterpenoids present in *A. marmelos* may be the reason for this anti- arthritic activity. Hence, *A. marmelos* can be used as an anti-arthritic agent.[41]

Ricinus communis (Eranda) leaf extract shows a significant anti-arthritic effect at the 200mg/kg and 400mg/kg dose levels. It might be due to the presence of phytochemicals such as flavonoids and saponin.[42] The results of 80% methanolic extract (500mg/kg) and total flavonoids fractions (50mg/kg) were at par with diclofenac sodium (20mg/kg). *Ricinus communis* leaves have anti-inflammatory potential and flavonoids dominate this activity in the extract.[43]

Curculiginis orchioides (Pashanabheda) curculigoside exhibited significant anti-arthritic activity in vivo and in vitro. This may be mediated by inhibition of pro-inflammatory cytokine release and downregulation of JAK/STAT signalling pathway proteins, as well as an increase in NF-κB and IκB expression. Findings from this study suggest that curculigoside could be regarded as a potential candidate drug for arthitis treatment. [44]

The extract of *Boerhaavia diffusa* (Punarnava) possesses potentially useful anti-arthritic activity in the Complete Freunds Adjuvant model. According to one study, 1000mg petroleum ether extract of *B. diffusa* roots produced an 81.58 percent response when compared to the standard drug (Indomethcin), while 500mg petroleum ether extract of *B. diffusa* roots produced a 41.92 percent response when compared to the standard.[45] Anti-inflammatory effect of *B. diffusa* was evaluated in rats by Sudhamadhuri and Kalasker.[46] Aqueous extracts were prepared from the plant leaves and their activity was determined on subacute inflammation (cotton pellet induced granuloma) and acute inflammation (carrageenan induced paw edema) in rats. Pre-administration of the extracts (200 and 400mg/kg) to the rats resulted in dose-dependent anti-inflammatory activity against sub-acute as well as acute inflammation. It was concluded that the above effects of the extracts were probably due to inhibition of chemical mediators of inflammation.

Treatment with *Abrus precatorius* (Gunja) was found to possess potent anti-arthritic activity with the least toxicity (no ulcerogenic) and the treatment significantly inhibited the development phase of arthritis, which is further supported by its radiographic analysis. Its anti- inflammatory effect was comparable to that of indomethacin (10mg/kg).[47]

Adhatoda vasica L. is an indigenous herb belonging to family Acanthaceae. The plant has been used in the indigenous system of medicine in worldwide as herbal remedy for treating various diseases including rheumatism and rheumatic painful inflammatory swellings. The anti-inflammatory potential of ethanolic extract has been determined by using carrageenan-induced paw edema assay, formalin-induced paw edema assay in albino rats. The ethanolic extract of *Adhatoda vasica* produced dose dependent inhibition of carrageenan and formalin-induced paw edema.[48]

The ethyl acetate and methanol extracts of the root of *S. cordifolia*, when tested in rats, using the carrageenan-induced edema model, both produced anti-inflammatory effects. Nevertheless, the effect of the ethyl acetate, at a dose of 600mg/kg, was equivalent to that of indomethacin. In addition, the ethyl acetate extracts of the aerial parts and root of this species exhibited substantial central and analgesic activity, employing the acetic acid induced writhing and hot plate methods.[49] An aqueous extract of S. cordifolia leaves was examined in animal models for their pharmacological properties and found to possess anti-inflammatory and analgesic functions, with low acute toxicity in mice. Some experimental evidence suggested the latter effects are mediated via interference with cyclooxygenase pathways.[50]

Ethanol and aqueous extracts of aerial parts of *S. rhombifolia* was reported to be useful in the treatment of arthritis.[51] The ethanol extract (95%) of aerial parts of S. rhombifolia possesses anti-inflammatory activity in Het-Cam assay and inhibit NF-Kappa B activation (100µg/ml) using cell culture of CA-Hela.[52]

Clove essential oil and eugenol derived from *S. aromaticum* have been documented to possess useful analgesic, anesthetic, and antiseptic effects and are therefore commonly used in dentistry.[53] In addition to that, they showed an anti-inflammatory efficacy against murine macrophages by suppressing the pro-inflammatory cytokines production[54] and eugenol prohibited IL-8 production enhancement against human gingival fibroblasts (HGF) but not against skin keratinocytes (HaCat) or periodontal ligament fibroblasts (HPLF).[55]

A study result has confirmed that extract of *A. indica* leaves at a dose of 200 mg/kg, p.o., showed significant anti-inflammatory activity in cotton pellet granuloma assay in rats.[56] Other study results revealed that neem leaf extract showed significant anti-inflammatory effect but it is less efficacious than that of dexamethasone[57] and study results suggest that nimbidin suppresses the functions of macrophages and neutrophils relevant to inflammation.[58]

Earlier finding showed immunomodulator and anti-inflammatory effect of bark and leave extracts and antipyretic and anti-inflammatory activities of oil seeds.[59,60] Experimentation was made to evaluate the analgesic activity of neem seed oil on albino rats and results of the study showed that neem seed oil showed significant analgesic effect in the dose of 1 and 2mL/kg and oil has dose-dependent analgesic activity.[61]

Another study was made to investigate the anti-inflammatory effect of neem seed oil (NSO) on albino rats using carrageenan-induced hind paw oedema and results revealed that NSO showed increased inhibition of paw oedema with the progressive increase in dose from 0.25mL to 2mL/kg body weight. At the dose of 2mL/kg body weight, NSO showed maximum (53.14%) inhibition of oedema at 4 hour of carrageenan injection.[62]

The outcome of the clinical study

Pankajakasthuri orthoherb cream/thermagel is a new herbal formulation that has clinically proven its capacity to combat osteoarthritis.

Acknowledgments

Authors give adored Pranams to “Aadhyathma Chinthalayesan”, Chinthala Ashram, Pothencode, Trivandrum, Kerala, India for his benevolence and blessings. We sincerely acknowledge Pankajakasthuri Herbal Research Foundation/Pankajakasthuri Ayurveda Medical College & PG Centre, Kattakada, Thiruvananthapuram, Kerala, India, and Pankajakasthuri Herbals India Pvt. Ltd, Poovachal, Kattakada, Thiruvananthapuram, Kerala, India for providing necessary support to conduct studies. Further, we thank all the Directors and staffs of Pankajakasthuri Herbal Research Foundation, Pankajakasthuri Ayurveda Medical College & PG Centre and Pankajakasthuri Herbals India Pvt. Ltd for their supports to complete this clinical trial smoothly.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

References

1. Lindler BN, Long KE, Taylor NA, et al. Use of Herbal Medications for Treatment of Osteoarthritis and Rheumatoid Arthritis. *Medicines*. 2020;7(11):67.

2. CDC. Osteoarthritis. USA: CDC; 2019.
3. Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. *Ann Phys Rehabil Med*. 2016;59(5–6):333–339.
4. de Cássia da Silveira E Sá R, Andrade LN, Dos Reis Barreto de Oliveira R, et al. A review on anti–inflammatory activity of phenylpropanoids found in essential oils. *Molecules*. 2014;19(2):1459–1480.
5. Gay NJ, Symmons MF, Gangloff M, et al. Assembly and localization of Toll–like receptor signalling complexes. *Nat Rev Immunol*. 2014;14(8):546–558.
6. Benly P. Role of histamine in acute inflammation. *J Pharm Sci Res*. 2015;7(6):373–378.
7. Reinke JM, Sorg H. Wound repair and regeneration. *Eur Surg Res*. 2012;49:3543.
8. Borges MC, Vinolo MA, Crisma AR, et al. High–fat diet blunts activation of the nuclear factor–κB signaling pathway in lipopolysaccharide–stimulated peritoneal macrophages of Wistar rats. *Nutrition*. 2013;29(2):443–449.
9. Park SK, Park SJ, Park SM, et al. Inhibition of Acute Phase Inflammation by Laminaria japonica through Regulation of iNOS–NF– κ B Pathway. *Evid Based Complement Alternat Med*. 2013;2013:439498.
10. Pashmforosh M, Rajabi Vardanjani H, Rajabi Vardanjani H, et al. Topical Anti–Inflammatory and Analgesic Activities of Citrullus colocynthis Extract Cream in Rats. *Medicina*. 2018;54(4):51.
11. Dhande PP, Gupta AO, Jain S, et al. Anti–inflammatory and Analgesic Activities of Topical Formulations of Pterocarpus Santalinus Powder in Rat Model of Chronic Inflammation. *J Clin Diagn Res*. 2017;11(7):FF01–FF04.
12. Selvarani K, Bai GVS. Anti–arthritic activity of Cayratia pedata leaf extract in Freund's adjuvant induced arthritic rats. *Int J Res Plant Sci*. 2014;4(2):55–59.
13. Gomes A, Bhattacharya S, Chakraborty M, et al. Anti–arthritic activity of Indian monocellate cobra (Naja kaouthia) venom on adjuvant induced arthritis. *Toxicon*. 2010;55(2–3):670–673.
14. Kanagasanthosh K, Shanmugapriyan S, Kavirajan V. Evaluation of acute toxicity, anti–inflammatory activity and phytochemical screening of ethanolic extract of Azadirachta indica leaves. *Int J Res Dev Pharm*. 2015;4(5):1737–1742.
15. Szunerits S, Boukherroub R. Heat: A Highly Efficient Skin Enhancer for Transdermal Drug Delivery. *Front Bioeng Biotechnol*. 2018;6:15.
16. Mulla W, More S, Jamge SB, et al. Evaluation of anti–inflammatory and analgesic activities of ethanolic extract of roots Adhatoda vasica Linn. *Inter J Pharm Tech Res*. 2010;2:1364–1368.
17. Kumar S, Vandana, Udaya A, et al. Analgesic, Anti–inflammatory and Anti–Pyretic Effects of Azadirachta indica (Neem) Leaf Extract in Albino Rats. *Inter J Sci Res*. 2015;4:713–721.
18. Naik MR, Bhattacharya A, Behera R, et al. Study of anti–inflammatory effect of neem seed oil (Azadirachta indica) on infected albino rats. *J Health Res Rev*. 2014;1:66–69.
19. Arul V, Miyazaki S, Dhananjayan R. Studies on the anti–inflammatory, antipyretic and analgesic properties of the leaves of Aegle marmelos Corr. *J Ethnopharmacol*. 2005;96(1–2):159–163.
20. Benni JM, Jayanthi MK, Suresha RN. Evaluation of the anti–inflammatory activity of Aegle marmelos (Bilwa) root. *Indian J Pharmacol* 2011;43(4):393–397.
21. Ilavarasan R, Mallika M, Venkataraman S. Anti–inflammatory and free radical scavenging activity of Ricinus communis root extract. *J Ethnopharmacol*. 2006;103(3):478–480.
22. Taur DJ, Waghmare MG, Bandal RS, et al. Antinociceptive activity of *Ricinus communis* L. leaves. *Asian Pac J Trop Biomed*. 2011;1(2):139–141.
23. Franzotti EM, Santos CV, Rodrigues HM, et al. Anti–inflammatory, analgesic activity and acute toxicity of *Sida cordifolia* L. (*Malva–branca*). *J Ethnopharmacol*. 2000;72(1–2):273–277.
24. Kanth VR, Diwan PV. Analgesic, anti–inflammatory and hypoglycaemic activities of Sida cordifolia. *Phytother Res*. 1999;13(1):75–77.
25. Dhara AK, Suba V, Sen T, et al. Preliminary studies on the anti–inflammatory and analgesic activity of the methanolic fraction of the root extract of Tragia involucrata Linn. *J Ethnopharmacol*. 2000;72(1–2):265–268.
26. Hareendran Nair J, Shan Sasidharan. *In–vivo* studies to manifest the potent anti–inflammatory and analgesic effect of the topical formulation, Pankajakasthuri orthoherb cream/thermagel upon single application in wistar albino rats. *Pharm Pharmacol Int J*. 2021:9(5):201–208.
27. Hareendran Nair J, Shan Sasidharan. Dermal irritation study of Pankajakasthuri orthoherb cream/thermagel, a potent polyherbal antiinflammatory and analgesic formulation for topical application in healthy New Zealand white rabbits. *J Toxicol: Curr Res*. 2021;5:022.
28. Ardiyanto D, Triyono A, Widhi PRA, et al. Clinical trial of osteoarthritis jamu formula compare to piroxicam. *Health Sci J Indones*. 2016;7.
29. Heyneman CA, Lawless–Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs*. 2000;60(3):555–574.
30. Haroutiunian S, Drennan DA, Lipman AG. Topical NSAID therapy for musculoskeletal pain. *Pain Med*. 2010;11(4):535–549.
31. Ribeiro MD, Joel SP, Zeppetella G. The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage*. 2004;27(5):434–439.
32. Paice JA, Von Roenn JH, Hudgins JC, et al. Morphine bioavailability from a topical gel formulation in volunteers. *J Pain Symptom Manage*. 2008;35(3):314–320.
33. http://www.livestrong.com/article/115826–benefits–guggul
34. Gujral M, Sareen K, Tangri KK, **et al.** Antiarthritic and anti–inflammatory activity of gum guggul (Balsamodendron mukul Hook). *IndianJ Physiol Pharmacol*. 1960;4:267–273.
35. Arora RB, Kapoor V, Gupta SK, et al. Isolation of a crystalline steroidal compound from Commiphora mukul and its anti–inflammatory activity. *Indian J Exp Biol*. 1971;9:403–404.
36. Chopra Center Healing Wisdom.com. Patel S. Ayurvedic Approaches to Osteoarthritis–Part I. HealngWisdom.c2013.
37. Sharma PC, Yelne MB, Dennis TJ, et al. Database on medicinal plants used in Ayurveda. India, New Delhi: Central council of Research in Ayurveda and Siddha; 2001. p. 451.
38. Manisha R Sharma, Charmi S Mehta, et al. Multimodal Ayurvedic management for Sandhigatavata (Osteoarthritis of knee joints). *Ayu*. 2013;34(1):49–55.
39. Vaidya B. Nighantu Adarsha. NirgundyadiVarga. India, Vadodara: Gujarat Pustakalaya Sahayaka Sahakari Mandali; 1999. p. 803.
40. Chaturvedi GN, Singh RH. Experimental studies on the anti arthritic effect of certain indigenous drugs. *Indian J Med Res*. 1965;53:71–80.
41. Sivakumar G, Gopalasatheeskumar K, Gowtham K, et al. Phytochemical analysis, Antioxidant and Antiarthritic activities of different solvent extract of Aegle marmelos L. unripe fruit. R*esearch J Pharm Tech*. 2020;13(6):2759–2763.
42. Kabra MP, Rachhadiya RM, Shete RV. Pharmacological investigation of hydroalcholic extract of Ricinus communis leaves in arthritis induces rat. *Asian J Biomed Pharm Sci*. 2011;4:2231–2560.
43. Saini AK, Goya R, Gauttam VK, et al. Evaluation of anti–inflammatory potential of Ricinus communis Linn leaves extracts and its flavonoids content in Wistar rats. *J Chem Pharm Res*. 2010;2(5):690–695.

Citation: Nair HJ, Sreekumar GS, Satheesan S, et al. A pilot clinical study to manifest the efficacy of Pankajakasthuri orthoherb cream/thermagel in the treatment of patients diagnosed with osteoarthritis. *Int J Complement Alt Med.* 2022;15(1):20–26. DOI: 10.15406/ijcam.2022.15.00585

44. Tan S, Xu J, Lai A, et al. Curculigoside exerts significant anti arthritic effects in vivo and in vitro via regulation of the JAK/STAT/NF κB signaling pathway. *Mol Med Rep*. 2019;19(3):2057–2064.

45. Dapurkar VK, Sahu GK, Sharma H, et al. Anti–Arthritic Activity of Roots Extract of Boerhaavia diffusa in Adjuvant Induced Arthritis Rats. *Sch Acad J Pharm*. 2013;2(2):101–106.

46. Sudhamadhuri A, Kalasker V. Evaluation of anti–inflammatory effect of aqueous extract of Boerhaavia diffusa leaves in rats. *Int J Res Health Sci*. 2014;2:517–521.

47. Sudaroli M, Chatterjee TK. Evaluation of red and white seed extracts of Abrus precatorius Linn. against freund's complete adjuvant induced arthritis in rats. *J Med Plant Res*. 2007;1(4):086–094.

48. Wahid a Mulla, Suyog D More, Suraj B Jamge, et al. Evaluation of anti–inflammatory and analgesic activities of ethanolic extract of roots Adhatoda vasica Linn. *Inter J Pharm Tech Res*. 2010;2:1364–1368.

49. Kanth VR, Diwan PV. Analgesic, antiinflammatory and hypoglycaemic activities of Sida cordifolia. *Phytother Res*. 1999;13:75–77.

50. Franzotti EM, Santos CV, Rodrigues HM, et al. Anti–inflammatory, analgesic activity and acute toxicity of Sida cordifolia L. (Malva–branca). *J Ethnopharmacol*. 2000;72:273–277.

51. Gupta SR, Nirmal SR, Patil RY, et al. Anti–arthritic activity of various extracts of Sida rhombifolia aerial parts. *Nat Prod Res*. 2009;23:689–695.

52. Dunstan CA, Noreen Y, Serrano G, et al. Evaluation of some Samoan and Peruvian medicinal plants by prostaglandin biosynthesis and rat ear oedema assay. *J Ethnopharmacol*. 1997;57:35–56.

53. Chaieb K, Hajlaoui H, Zmantar T, et al. The chemical composition and biological activity of clove essential oil, Eugenia caryophyllata (Syzigium aromaticum L. Myrtaceae): a short review. *Phytother Res*. 2007;21(6):501–506.

54. Bachiega TF, de Sousa JP, Bastos JK, et al. Clove and eugenol in noncytotoxic concentrations exert immunomodulatory/anti–inflammatory action on cytokine production by murine macrophages. *J Pharm Pharmacol*. 2012;64(4):610–616.

55. Koh T, Murakami Y, Tanaka S, et al. Re–evaluation of anti–inflammatory potential of eugenol in IL–1β–stimulated gingival fibroblast and pulp cells. *In Vivo*. 2013;27(2):269–273.

56. Chattopadhyay RR. Possible biochemical mode of anti–inflammatory action of Azadirachta indica A. Juss. in rats. *Indian J Exp Biol*. 1998;36(4):418–420.

57. Mosaddek ASM, Rashid MMU. A comparative study of the anti–inflammatory effect of aqueous extract of neem leaf and dexamethasone. *Bangladesh J Pharmacol*. 2008;3(1):44–47.

58. Kaur G, Sarwar Alam M, Athar M. Nimbidin suppresses functions of macrophages and neutrophils: relevance to its antiinflammatory mechanisms. *Phytother Res*. 2004;18(5):419–424.

59. Arora N, Koul A, Bansal MP. Chemopreventive activity of Azadirachta indica on two–stage skin carcinogenesis in murine model. *Phytother Res*. 2011;25(3):408–416.

60. Biswas K, Chattopadhyay I, Banerjee RK, et al. Biological activities and medicinal properties of Neem (Azadirachta indica). *Curr Sci*. 2002;82(11):1336–1345.

61. Kumar S, Agrawal D, Patnaik J, et al. Analgesic effect of neem (Azadirachta indica) seed oil on albino rats. *Int J Pharma Bio Sci*. 2012;3(2):P222–P225.

62. Naik M R, Bhattacharya A, Behera R, et al. Study of anti–inflammatory effect of neem seed oil (Azadirachta indica) on infected albino rats. *J Health Res Rev*. 2014;1(3):66–69.

Citation: Nair HJ, Sreekumar GS, Satheesan S, et al. A pilot clinical study to manifest the efficacy of Pankajakasthuri orthoherb cream/thermagel in the treatment of patients diagnosed with osteoarthritis. *Int J Complement Alt Med.* 2022;15(1):20–26. DOI: 10.15406/ijcam.2022.15.00585