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# A Systematic Review on *Panchakarma*-Based Ayurveda Treatment in *Janu Sandhigata Vata*

**Review Article**

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## Abstract

*Janu Sandhigata Vata* or knee osteoarthritis (KOA) causes chronic pain, stiffness, immobility and affects daily life. *Panchakarma*-based Ayurvedic treatment is popular in arthritis. The present study has done a systematic review on effectiveness and safety of *panchakarma*-based treatment in chronic KOA. The study searched for double-arm randomized comparative trials (RCoTs) with human subjects (age ≥ 18 years) explicitly diagnosed with KOA in fourteen electronic databases including MEDLINE, PubMed Central, Cochrane, Ayush Research Portal for indexed research and clinical trials published till September 30, 2022. At least one patient-centred primary outcome, namely pain, physical function, global improvement according to OMERACT III were eligible. Risk-of-bias analysis was done independently by the two authors using the revised Cochrane risk-of-bias tool for randomized trials. Effect size as standardized mean differences between treatments were estimated for pain and stiffness. The inclusion criteria screened 10 RCoTs. The RCoT which used manual therapies in a multimodal ayurvedic care against conventional care had overall low risk of bias. Remaining 9 RCoTs compared the treatment outcomes of different *panchakarma*-based treatment with and without pharmacological interventions. In 3 RCoTs, effect size on pain and stiffness were medium to large and significant ($P<0.01$). Only 3 RCTs reported safety concerns and no serious adverse outcomes related to intervention were noted. Sudation techniques and enema therapy used as standalone or in multimodal ayurvedic care showed benefit in KOA. Future studies on the long-term efficacy and safety goals aligned to psychosomatic record of patients are required for personalized Ayurveda multimodal care.

**Key Words:** Randomized Comparative Trials, Pain, Stiffness, Oleation, Sudation, Enema.

## Introduction

It is estimated that by 2050, about 40 million people worldwide will have severe disability from chronic osteoarthritic diseases (1). *Janu Sandhigata Vata* or knee osteoarthritis (KOA) is the most common form of arthritis in India and one of the leading causes of functional impairment, disability affecting the quality of life (2,3). The risk factors driving the onset of KOA can be idiopathic or non-idiopathic in nature (2,4,5). Mechanical overload, trauma, age related wear and tear causes degenerative changes in the articular cartilages of the knee joint. Deterioration of the osseous structures of the knee and its surroundings, are associated with inflammatory changes. Multiple inflammatory mediators (plasma C-reactive protein, prostaglandins, leukotrienes, growth factors and cytokines) trigger the action of matrix metalloproteinases, cyclooxygenase and prostaglandin E and thus causing cartilage breakdown and collagen destruction. These endless, self-perpetuating cycle of local tissue damage are faster than the tissue repair process, thus making KOA a chronic disorder (6). The whole process of destruction leads to deformed bone remodelling, osteophyte formation, joint space narrowing, weakening of periarticular muscles, and synovial effusion result in the chronic pain, stiffness, swelling and crepitus at the knee joint (2).

Standard conventional treatment of KOA is mostly symptomatic in nature and ranges from medications, electrical stimulation, assistive devices, intra-articular knee injections and surgical intervention (2,7). Commonly used medicines in KOA are non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine, corticoids, and viscosupplements used to improve mobility and reduce arthritic pain. Arthroscopy, cartilage repair, osteotomies, and partial or total arthroplasty are the surgical intervention in

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severe KOA (2,7). Nowadays, regenerative medicine in KOA treatment is under test and need more clinical evaluation for human use (8). But the general line of treatment also has risk of adverse effects, abusive potentials and some are highly expensive to a larger mass of patient population (7). Apart from the general treatment, there are evidenced based approach with traditional medicines and care in KOA. Countries such as India, China use their own ancient traditional ways of treating most diseases by using medicinal plants, herbs and other therapeutic techniques. The World Health Organization (WHO) is recommending to boost the use of medicinal systems of Ayurveda medicines along with the usual mode of treatments (8).

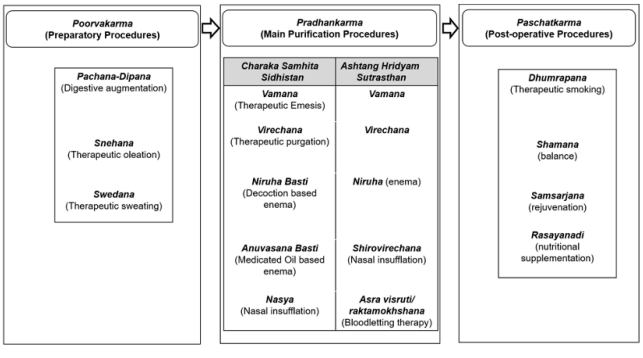
Ayurveda is India's ancient traditional indigenous medicinal system acknowledged by the World Health Organization (8,9). The three ancient compendia, *Charaka Samhita*, *Sushruta Samhita* and *Ashtang Hridyam,* on Indian Ayurvedic medicinal system elaborated on the methods of clinical diagnosis, medicine, surgery, natural sources of drugs and pharmaceutics and are followed in modern day practice and research (10,11,12,13,14). Ayurveda is claimed to be effective in treating chronic diseases of the musculoskeletal system (15, 16,17, 18,19, 20, 21, 22). In India, an estimated 50-60% of patients suffering from arthritis seek Ayurvedic care (13). The diagnosis of KOA in Ayurveda cannot be equated directly with Western conventional treatment entities. KOA belongs to the cluster of diseases prevalent under *vata* (23,24,25). Ayurveda observes health and disease as a continuum, and maladaptive life style, trauma, triggering aggravation of the principles of *vata* and thereby causing *rukshata* (dryness), *laghutva* (lightness), *saushirya* (porosity), and *kharatva* (coarseness) into the joints affecting normal articulation during movement and locomotion, producing *sandhi-shula* (knee pain), *shotha* (swelling), *stabdhata* (stiffness), *atopa* (crepitus) (22). Diminution and regulation of the *vata* (aggravated principle of kinetic force) is the basis of Ayurvedic treatment for KOA comprising individually tailored interventions, including medication, purification measures, lifestyle and nutritional advice, dietary supplements (23, 24, 26).

Ayurveda usually normalises the *vata* imbalance through *samana chikitsa* (palliative care) including oral medications, dietary supplements, massages. But excessive aggravation of *vata* in the joints required the forceful expulsion from the body through *samshodhana chikitsa* (purification). *Panchakarma*-based treatment is one of the elements of multimodal Ayurvedic treatment for sam*shodhana* and restoring body homeostasis through several therapeutic techniques appropriate for eradicating the imbalances in disease (26). Generally, the five main therapeutic procedures called as *pradhankarma* in *panchakarma* elaborated in *Charaka Samhita* are *vamana karma* (emesis), *virechana karma* (purgation), *anuvasana basti* (oil-based enema), *niruha basti* (decoction-based enema) and *nasya karma* (nasal insufflation therapy) (10, 26). *Asruvisruti/raktamokshana* (bloodletting) was also mentioned as an element of purification treatment in the *Astang Hridyam* (27) (Figure 1).

Ayurvedic treaties prescribed the use of the three manual treatments namely *snehana* (oleation-based massage), *swedana* (sudation) and *anuvasana basti* (oil-based enema) with the underlying principle of channelizing the disease-causing toxins from the affected knee joints to eliminatory routes for expulsion comprise the *panchakarma*-based treatment. In KOA, *snehana* and *swedana* are given as *poorvakarma* (preparatory phase) in *panchakarma* or as independent single intervention depending upon the severity of the symptom (26,28,29). In Ayurveda, *samshodhana* (purification) therapy by removal of aggravated metabolic intermediates and toxins causing diseases is believed to be essential for *shamana chikitsa* (palliative care) (26).

Earlier a systematic review and meta-analysis conducted on 238 retrieved records from the digital databases on randomized control, randomized cross-over, cluster randomized and non-randomized studies on Ayurvedic intervention in OA showed that largely studies were confined to testing efficacy of ayurvedic herbs and medicated formulations in established joint pathologies (16). Some of the important questions related to KOA management with *panchakarma*-based therapies are yet to be answered. These include the choice of manual therapy, the significance of a selected therapy or combination of therapies related to patient specific conditions i.e., treatment personalization, duration, safety of interventions in standalone or integrative treatment. But, at first evidence-based findings on the efficacy and safety of the *panchakarma*-based treatment strategies in treating KOA in the clinical trials is required to be systematically evaluated. The present study has conducted a non-meta-analytic systematic review on the effectiveness and safety of *panchakarma* based therapy in chronic KOA patients from double-arm randomized comparative trials (RCoT). RCoTs were considered for inclusion of trials for comparing between the efficacy of different *panchakarma* based treatments as well as with standard conventional care. KOA was chosen since it is most common in the Indian population and has negative impact on the physical functioning of patients.

**Figure 1: Therapeutic Procedures under the general line of treatment during *Panchakarma***



# Materials & Methods

## Eligibility Criteria

### Studies

Double arm randomized comparative trials (RCoTs) without meta-analysis were eligible for the review.

### Subjects

Studies in adult human subjects (age≥ 18 years) irrespective of gender and explicitly diagnosed with KOA according to the classification criteria of the American College of Rheumatology (30) or any other criteria were eligible. KOA found in the title, abstract, keywords or cited in the literature were included.

### Interventions

Experimental interventions overtly labelled as *panchakarma* and Ayurveda were included. As *panchakarma* is under Ayurvedic medicinal system, thus Ayurveda as intervention was also included in the search. This was done to include any trials non-explicitly administering *panchakarma* context-based treatments. *Panchakarma*-based treatment that are recommended in the ancient Ayurvedic texts for treatment of aggravated *vata* namely *snehana* (oleation), *swedana* (sudation), *basti* (enema) and *virechana* (mild purgation) were included. Sudation therapy and oleation therapy are generally the preoperative procedures under *panchakarma*-based treatment regime essential for elimination of vitiated *vata* (25, 29). Although bloodletting was not mentioned as a recommended treatment in *Charaka Samhita*, but it was included in the study due to use in vitiated blood induced joint pain. Further, explicit labelling on *panchakarma* and Ayurveda was used to exclude treatment modalities used in other traditional systems with a different name. Such as leech therapy used as purification procedure in *panchakarma* is also practiced in traditional Chinese medicines and other early 19th century European systems (31,32). Thus, in order to exclude the latter cases, explicit labelling of *panchakarma* and Ayurveda was considered. Nowadays, Yoga is considered as one the treatment modalities under Ayurveda, although evidences are missing in ancient Ayurvedic texts of *Charaka Samhita,* Therefore, studies using yoga as a single intervention for KOA were excluded from this review. Controls to the experimental intervention were either standard conventional care or any comparator Ayurvedic interventions.

### Outcome Measures

Studies assessing at least one patient-centred primary outcome, namely improvement in pain, physical function, or global improvement according to OMERACT III (33) were eligible. Outcomes such as quality of life, stiffness, imaging, and safety of the intervention were secondary.

### Search Methods

Fourteen electronic databases were searched for original research articles and clinical trials published till September 30, 2022. The search comprised databases and registers including MEDLINE, PubMed Central, Cochrane, Cam Quest, DOAJ, DHARA, Ayush Research Portal, Annotated Bibliography of Indian Medicine, clinicaltrials.gov and 5 other databases. The keywords used for the identification of studies were 'double-arm randomized control trial', '*panchakarma*', 'Ayurveda', 'Ayurved*', '*snehana*', '*swedana*', '*basti*', '*virechana*', '*raktamokshana'*, '*jalaukavacharana*', 'leech therapy' combined with KOA search terms like, 'knee osteoarthritis', 'janu sandhigata vata', '*sandhigata vata*', '*sandhivata*', 'Ayurveda manual treatment'. *Janu sandhigata vata* is the *Sanskrit* terminology used by Ayurvedic physicians for KOA. The search strategy based on the keywords was applied to all databases as necessary and were searched in the title, abstract, keywords and text. Trials in humans were included. Two review authors were independently involved in the identification of articles during the search and later in the screening process. Duplicate articles were removed in the identification stage. Ongoing trials and completed trials lacking reporting of outcome measures in the online clinical registers were also removed. Next, studies which had titles only were removed. The abstracts of the remaining studies were then reviewed under the already given criteria. Full-text articles were retrieved for potentially eligible studies and were read by the review authors to finally screen based on the eligibility criteria. If there were any differences between the two authors, the third review author assisted in reaching a final judgement. The PRISMA 2020 guidelines were followed during the identification and screening stages (34).

### Risk of Bias Analysis

The authors collected the information on subjects, study design, experimental interventions, comparator, outcome measures and the results of the eligible studies after the screening. Next, risk of bias in each study was assessed independently by the two authors using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (35). The risk of bias was evaluated mainly under five domains, which were bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported results and others bias if present. and the risk of bias was rated as (1) low risk of bias, (2) unclear, (3) high risk of bias. Briefly, the bias tool operated with signalling questions in each domain and the probable single response in either yes, probably yes, probably no, no or no information. The responses were fed into an algorithm provided by the tool to reach the judgement on the risk of bias as minimal risk or some concerns or high risk. Based on the judgments of the given five domains, a final call on the risk of bias of the entire study was reached with the tool algorithm. In case any discrepancy arose between the two authors, it was

rechecked and discussed with the third author and a final decision was reached.

**Data Analysis**

Effect sizes for outcomes measures on pain and stiffness were estimated as standardized mean differences (SMD) with 95% confidence interval and P value. The SMD was calculated as the differences of the mean change from baseline divided by pooled SD between the comparing groups as presented in the RCoTs. If instead of SD, standard error and confidence interval were provided, SD was calculated and used for SMD estimation. Due to small sample size, the overall effect was expressed in Hedge's g. Magnitudes of the overall effect size were compared as: SMD of 0.2–0.5: small; SMD 0.5–0.8: medium; and SMD > 0.8: large effect size.

# Results

**Literature Search**

A total of 339 records were identified in the search. Out of which 156 records were assessed for eligibility during screening and 10 RCoT (21 36,37,38,39, 40,41,42, 43, 44) were included for the study according to the criteria. The details are given in the PRISMA flow chart (Figure 2).

The RCoTs included a total of 521 subjects between 30 to 80 years of age. Although the inclusion criteria of all studies mentioned both male and female patients, but only 4 RCoTs have given the number of male & female participants (Table 1). 5 RCoTs reported the number of dropout post-randomization and the remaining 5 RCoTs did not report. Only one RCoT reporting the drop-out has also reported about missing outcome data and the authors of the remaining 4 RCoTs were not contacted for missing data retrieval. Some adverse reactions in the Ayurveda treatment group were noted in 2 RCoTs, although the events did not lead to hospitalization.

**Figure 2: PRISMA Flow Diagram (34)**

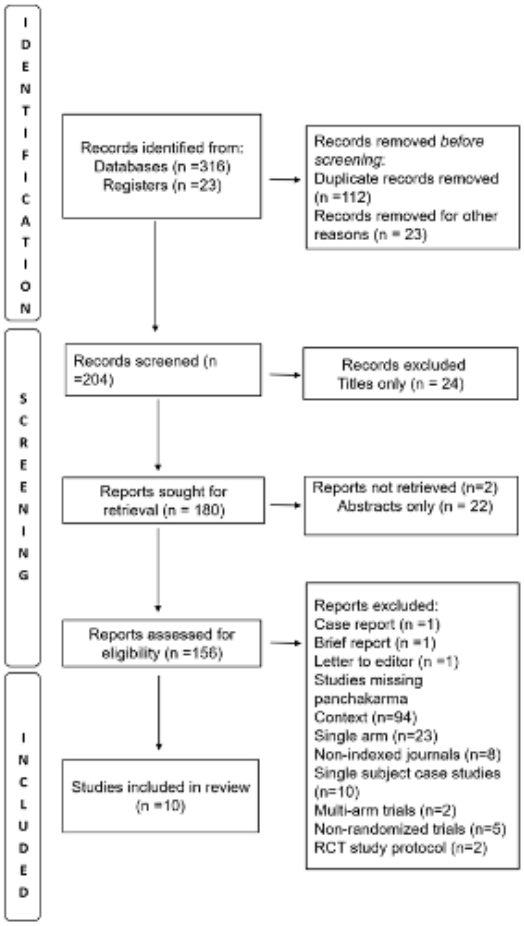



**Table 1: Characteristic Eligibility Criteria of RCTs on *Panchakarma* Based Treatment in Knee Osteoarthritis**

| Reference Origin | No. of Patients | Inclusion Criteria | Exclusion Criteria | Experimental Intervention | Comparator Intervention | Duration (days) | Outcome measures | Adverse Effect | Dropouts |
|---|---|---|---|---|---|---|---|---|---|
| Sharma & Bhattachary-ya, 2013 [36] | 40 (EI=20 CI=20) | Age: 30-60 yrs., Patients with classical symptoms of Janu Sandhigata Vata, Disease chronicity < 1 year | Chronicity of disease > 1 year, lactating and pregnant women, complications including contractures, nodules, septic arthritis etc., Secondary malignant conditions and traumatic conditions, suffering from cardio-pulmonary diseases, hypertension, bleeding disorders, diabetes etc and other serious systemic and complicated diseases. | Rasana Panchaka Kashaya with 50ml Prasarini Taila + Matra Basti | Rasana Panchaka Kashaya 25ml twice daily | 30 | Joint Pain (Sandhishula), Joint Swelling (Sandhishotha), Pain in range of motion (Prasaranaakun-janayo vedana), Lysholm Knee Score, Range of Motion | No toxicity or side effects noted | 7 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pooja & Bhatted, 2013 [37] | 30 (EI=15 CI=15) | Age: 30 - 80 years with signs and symptom of osteoarthritis | Cases of severe systemic disorders, infections like bone tuberculosis and diabetes. | Rasnasaptaka kvatha, Asvagandha curna, satavari curna, Madhuyasti curna, Copacini curna + Janu Basti with dashamuladi taila | Rasnasaptaka kvatha, Asvagandha curna, satavari curna, Madhuyasti curna, Copacini curna | 30 | Pain, Swelling, Stiffness, Crepitus | Not reported | Not reported |
| D'souza & Acharya, 2014 [38] | 68 (EI=35 CI=33) | Age: <=70 yrs. Patients reporting for first time & patients with negligible response treated otherwise | Trauma and fractures-induced KOA, with systematic diseases. Not fit for leech therapy, mental illness, lactating and pregnant mothers. | Non-poisonous Leech (Nirvisha Jalauka) (EI) | Nirgundi Taila with cotton bandage (Janu Vestana) (CI) | 14 | Pain, Stiffness, Range of Motion | No major adverse effects noted | 6 (EI: 4; CI:2) |
| Arya et al. 2018 [39] | 42 (EI=22 CI=20) | Age: 40-70 yrs., Patients with Janu Sandhigata Vata according to the Ayurveda criteria of knee osteoarthritis, Cases of primary knee arthritis | Patients with secondary KOA, history of traumatic injury, systemic illness like diabetes mellitus, liver and cardiac diseases, tuberculosis, rheumatoid arthritis, gout | Upanaha Sweda + Vatari Guggulu (EI) | Upanaha Sweda (CI) | 60 | Pain, Swelling, Stiffness, Tenderness, Crepitus, and Ranges, X-ray findings | Not reported | 9 (EI :7; CI:2) |
| Kessler et al. 2018[21] | 151 EI:77 CI:74 | Age: 40-70 yrs., pre-diagnosed knee OA using ACR criteria by an orthopaedic surgeon and radiologist; radiologic abnormalities on an X-ray or an MRI | congenital dysplasia, rheumatoid arthritis, autoimmune disorders, cancer, knee surgery, or knee arthroscopy, acute mental disorders, serious acute organic diseases, chronic co-morbidities, obesity grade II blood coagulation disorders, pregnancy/ nursing; other knee OA treatment in 4weeks prior enrolment, paracetamol, over-the-counter NSAIDs usage, CAM therapies, invasive procedures in the affected joint in 12 weeks prior to enrolment or planned after enrolment | Multi-modal Ayurvedic intervention using targeted manual therapies, massages, ayurvedic nutrition, general and precise lifestyle guidance, knee-specific yoga posture recommendations, and daily self-applied knee massage. (EI) | Customised conventional care using quadriceps strengthening exercises, knee-specific physiotherapy, occupational therapy, individualized knee exercises, dietary recommendations for overweight participants, and, if necessary, the administration of long-term pain medication in accordance with the recommended guidelines. (CI) | 12 weeks or 90 days (Over 15 sessions) | Pain, stiffness, and function with WOMAC indexing, self-reported secondary outcomes on pain disability index (PDI), numeric rating scale (NRS), additional questions on pain and sleep quality, a pain experience scale (SES), health-related quality of life (SF-36), and the profile of mood states | 137 adverse events in 73 patients (59.7% in Ayurvedic group and 36.5% in convention al group, had more than one adverse event). | At 6 and 12 weeks, 4 (EI:1; CI:3), At 6 months 5 (EI:1; CI:4), 6 (EI:1; CI:5) at 12 months. |
| Prathibha et al. 2019 [40] | 30 (EI=15 CI=15) | Age: 40-70 yrs. and who were fit for Pinda Sweda and Upahana Sweda | skin allergies/skin diseases on knee joint, with systemic conditions such as gouty arthritis, rheumatoid arthritis, psoriatic arthritis, and complicated arthritis, | Poorvakarma =Sthanika Abhyanga (Localised oleation); Pradhankarma= Patra Pinda Sweda (bolus of chopped leaves) | Poorvakarma= Sthanika Abhyanga (Localised oleation); Pradhankarma = Upanaha Sweda (poultice) | 21 | Pain (sandhishula), swelling (sandhishotha), Intolerance to touch (Saprshaasahisnuta) crepitus, stiffness (sandhstabdhata), range of motion | Not reported | Not reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rakesh et al., 2020 [41] | 40 (EI=20 CI=20) males:14 females:26 | Age: 35-70 yrs., Subjects with classical signs & symptoms of Janu Sandhigata Vata Subjects with osteophytic changes in X-ray, Joint space narrowing | Subjects with bony deformity, rheumatic heart disease, rheumatoid arthritis, gouty arthritis, other inflammatory joint conditions, any systemic illness inferring treatment | Janubasti with Mahavishagarb-ha Taila and Tab. Asthishrinkhal-a 500mg 1 T.I.D after food | Janubasti with Mahavishag-arbha Taila and Tab. Glucosamine Sulphate 500mg 1 T.I.D after food | 30 | Joint Pain (Sandhishula), Stiffness (Sthamaba), Crepitus (Sputana), Range of Movement, Tenderness | Not reported | Not reported |
| Reshmi et al., 2020 [42] | 40 (EI=20 CI=20) | Age: 30-70 yrs., Patients with classical diagnostic signs and symptoms of Janu Sandhigata Vata. Patients fit for Swedana | Patients of tuberculosis, rheumatoid arthritis, psoriatic arthritis, structural deformity and any other systemic diseases, patients unfit for swedana therapy. | Grihadhumadi Upanaha Sweda | Kottamchuk-kadi Upanaha Sweda | 15 | Swelling, Stiffness, Tenderness, VAS, ROM and WOMAC Index | Not reported | Not reported |
| Desai et al. 2021 [43] | 50 (EI=25CI =25) | Age: 40-70 yrs., Patients fulfilling the diagnostic criteria of Janu Sandhigata Vata Patients fit for *sthānika svedana karma* | Inflammatory arthritis, gouty arthritis, rheumatoid arthritis, fractures. Patients with skin diseases and open lesions at knee joints. | Poorvakarma = Sthanika Abhyanga with Tila Taila, Pradhana Karma = Upanaha Sweda with Koladi Yoga | Poorvakarma = Sthanika Abhyanga with Tila Taila, Pradhana Karma = Upanaha Sweda with Vachadi Yoga | 15 | Joint pain, joint inflammation, joint crepitus pain in movement, tenderness | Not reported | 10 patients from each group dropped out |
| Nakum et al., 2022 [44] | 30 EI=15 CI=15) | Age: 40-70 yrs.; both male & female; Patients with classical signs and symptoms of Sandhi Vata (Osteoarthritis) | Vatarakta, Amavata, Systemic Lupus Erythematous (SLE), Bone TB, diabetes, Psoriatic arthritis and other serious systemic disorders | Nirgundi Patra Pinda Sweda and Matra Basti with Ashwagandhadi Taila | Nirgundi Patra Pinda Sweda | 15 | Pain, swelling, tenderness, stiffness, pain at movement, Sandhi Sphutana | Not reported | Not reported |
| EI= experimental Intervention; CI= Comparator; | | | | | | | | | |

In 2 RCoTs (36, 38), no adverse and toxic effect were detected, and the remaining RCoTs did not report about any adverse effects if found or not found. The characteristics of the RCoTs were provided in details in Table 1.

One RCT has used Ayurveda manual therapies as part of the multimodal personalized Ayurvedic intervention for KOA against a standard conventional multimodal care. The manual therapies although explicitly not mentioned according to Ayurveda or *panchakarma* nomenclature, yet specified as massages, steam application designed and implemented by Ayurvedic clinicians, experts in treating KOA according to the ancient Ayurvedic literatures. Most trials witnessed a specific *panchakarma*-based manual intervention called sudation *swedana* accounting 5 from 9 RCoTs (39,40,42,43,44). Other *panchakarma*-based methods that were compared were *matra basti* in 2 RCoTs (36,44) and leech therapy in 1 RCoT (38). *Janu basti*, a combined *snehana* (oleation) and *swedana* (sudation) method specific to KOA treatment, was also given in 2 RCoTs (37, 41). In conjunction some trials tested diverse medicinal formulation with the *panchakarma*-based methods (36,37,39,41,42,43). The details on the characteristics of the RCoTs are mentioned in Table 1. Except one which was a holistic Ayurveda approach comprising manual therapies, not a single trial was found comparing *panchakarma*-based manual intervention against standard conventional Western medicinal treatment for KOA or placebo control under our search criteria. Each of these 9 RCoTs allocated different types and combination of *panchakarma*-based treatments or *panchakarma*-based treatments with ayurvedic-formulations under randomized comparative design and tested their efficacies in KOA. A classification based on treatment and their comparison was attempted and presented in Table 2 under four broad categories namely, sudation, identical ayurvedic formulation, non-identical ayurvedic formulation and leech therapy.

**Table 2: Categorization of Included RCTs**

| | Treatment 1 | | Treatment 2 |
|---|---|---|---|
| Sudation | *Upanaha Sweda* (Warm medicated paste in poultice) | vs. | *Patra Pinda Sweda* (Fomentation-based bolus of oil-roasted medicinal plant leaves) |
| | *Upanaha Sweda* | vs. | *Upanaha Sweda* + AF |
| | *Patra Pinda Sweda* | vs. | *Patra Pinda Sweda* + *Matra Basti*(enema) |
| Identical Ayurvedic Formulation (iAF) | iAF1 | vs. | iAF1+*Matra Basti* |
| | iAF2 | vs. | i AF2+*Janu Basti* |
| Blood letting | *Janu vestana* (Medicated knee bandage) | vs. | *Jaluakavacharana* (Leech therapy) |
| Non-identical medicinal formulation (nAF) | *Upanaha Sweda* + nAF1 | vs. | *Upanaha Sweda* + nAF2 |
| | *Upanaha Sweda* + nAF3 | vs. | *Upanaha Sweda* + nAF4 |
| | *Janu basti* + nAF5 | vs. | *Janu basti* + nAF6 |
| Multi-modal care | *Western Conventional Care* | vs. | *Ayurvedic treatment (manual therapies, massages, steam application as treatment components)* |

iAF1: Rasana Panchaka Kashaya; iAF2: Samanyadravya; nAF1: Grihadhumadi; nAF2: Kottamchukkadi; nAF3: Vachadi Yoga; nAF4: Koladi Yoga; nAF5: Glucosamine sulfate; nAF6: Asthhishrinkhala

Sudation group comprises 3 RCoTs in which a sudation treatment given to a patient group were compared either with another different sudation treatment or combined ayurvedic formulation with sudation, or with another *panchakarma*-based treatment (39,40,44). Identical ayurvedic formulation group included 2 RCoTs where an ayurvedic formulation was compared with its combination with a *panchakarma*-based treatment (36,37). Non-identical medicinal formulation group contains 3 RCoTs where different ayurvedic medicinal formulations were compared (41,42,43). Either of the treatment group in this category used the identical *panchakarma*-based therapy along with the differing medicines. Lastly, only one RCoT compared leech therapy with a medicated knee bandaging technique (38).

**Risk of Bias Analysis**

The risk of bias analysis with RoB2 tool on included 10 RCoTs is presented in Table 3. All RCoTs except one, showed high risk of overall bias. In randomization domain, 9 RCoTs had some concern and 1 RCoT presented high risk of bias. Regarding deviation from intended interventions 7 RCoTs had high risk of bias, 2 RCoTs had some concerns and 1 RCoT had low risk. 6 RCoTs showed high risk of bias for missing outcome data and 4 RCoTs possessed low risk. 9 RCoTs had high risk of bias in the measurement of outcome domain and 1 RCoT showed low risk. 1 RCoT had low risk on selection of reported results domain,7 RCTs had some concerns and 2 RCoTs had high risk of bias (Details in supplementary data).

**Effect size estimation**

Effect sizes expressed in SMD were presented for pain and stiffness in Table 4 and 5 respectively. Out of 10 RCoTs, it was possible to estimate SMDs on pain and stiffness outcomes from 7 and 5 RCoTs respectively. SMD could not be calculated from the rest of RCoTs as SD, SEM or CI on pain and stiffness were not reported. Only one RCoT had mentioned the multimodal Ayurvedic treatment as intervention against a multimodal conventional care. The remaining trials did not classify the treatment groups as intervention and comparator, rather they used the term comparative design between two treatments. So, the study categorization as in Table 2 was used to compare effect size of treatment outcome on pain and stiffness.

In Table 4, the multimodal Ayurveda treatment included manual therapies shows significant treatment outcome in both pain (SMD [[±95% CI]: 0.64 [0.32 0.97]; P<0.001) and stiffness (SMD [[±95% CI]: 0.63 [0.30 0.95]; P<0.001) in comparison to a standard conventional ayurveda care. The sudation group shows insignificant difference in effect size between *upanaha sweda* and *patra pinda sweda treatment* (SMD [±95% CI]: 0.121 [-0.576 0.818], P=0.734), whereas *patra pinda sweda* with *matra basti* has maximal effect size when compared to *patra pinda sweda* alone (SMD [±95% CI]: 2.139 [1.257 3.02], P=2.00e-6). SMD for pain was also estimated in the identical ayurvedic formulation group, where effect size was insignificant between *rasana panchaka kashaya* and the same applied *with matra basti* (SMD [±95% CI]:0.417 [-0.197 1.031], P=0.183). The effect size on pain was insignificant between *samana dravya* and *samanadravya* with *janu basti* (SMD [±95% CI]: 0.643 [-0.072 1.358], P=0.078). The effect size of *jalauakavacharana* with *janu vestana* was significant in the bloodletting therapy on pain outcome *(*SMD [±95% CI]: 1.855[1.260 2.439], P=7.82e-10*)*. The RCoT in the non-identical ayurvedic formulation groups showed high effect size in favour of *upanaha sweda* with *kottamchukkadi* than with *grihadhumadi* (SMD [±95% CI]:0.799 [0.167 1.432], P=0.013). The multimodal Ayurvedic treatment showed moderate effect size in comparison to standard care (SMD [±95% CI]:0.64 [0.32 0.97], P<0.001).

On stiffness outcome provided in Table 5, only 2 RCoTs using *patra pinda sweda* with *matra basti* vs *patra pinda sweda* and *jalaukavacharana* with *janu vestana* vs *jalaukavacharana* showed significant effect

size on stiffness outcome (SMD [±95% CI]: 2.239 [1.341 3.137], P=1.01e-06 & SMD [±95% CI]: 0.668 [0.166 1.173], P= 0.0096). The effect size in RCoTs with identical and non- identical ayurvedic formulations were insignificant (SMD [±95% CI]: 0.581 [-0.131 1.292], P=0.11 & SMD [±95% CI]: 0.287 [-0.324 0.898], P=0.357). The multimodal Ayurvedic treatment showed moderate effect size in comparison to standard care (SMD [±95% CI]:0.63 [0.30 0.95], P<0.001).

**Table 3: Assessment of Risk of Bias in the RCTs using Cochrane Risk of Bias Tool**

| Articles | Randomization Process | Deviations from the intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported results | Overall Bias |
|---|---|---|---|---|---|---|
| **Sharma & Bhattacharyya, *IAMJ* 2013** [36] | Some Concerns | High Risk | High Risk | High Risk | Some Concerns | High Risk |
| **Pooja & Bhatted, *Āryavaidyan* 2013** [37] | Some Concerns | Some Concerns | Low Risk | High Risk | Some Concerns | High Risk |
| **D'souza & Acharya, *Int J Res Ayurveda Pharm* 2014** [38] | Some Concerns | Some Concerns | High Risk | High Risk | High Risk | High Risk |
| **Arya et al., *Int J Ayurveda Pharm Res 2018*** [39] | Some Concerns | High Risk | High Risk | High Risk | High Risk | High Risk |
| **Kessler et al.; *Osteoarthritis Cartilage 2018*** [21] | Some Concerns | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk |
| **Pratibha et at., *Int J Res Ayurveda Pharm* 2019** [40] | Some Concerns | High Risk | Low Risk | High Risk | Some Concerns | High Risk |
| **Rakesh, et al. *JAIMS* 2020** [41] | High Risk | High Risk | High Risk | High Risk | Some Concerns | High Risk |
| **Reshmi et al., *JAIMS* 2020** [42] | Some Concerns | High Risk | High Risk | High Risk | Some Concerns | High Risk |
| **Desai et al., *IAMJ* 2021** [43] | Some Concerns | High Risk | High Risk | High Risk | Some Concerns | High Risk |
| **Nakum et al., *IRJAY* 2022** [44] | Some Concerns | High Risk | Low Risk | High Risk | Some Concerns | High Risk |

**Table 4: Effect Size Estimation: Pain**

| | ***Mean*** | ***SD*** | ***N*** | | ***Mean*** | ***SD/95% CI*** | ***N*** | ***SMD, 95% CI*** | ***P-value*** |
|---|---|---|---|---|---|---|---|---|---|
| ***Sudation*** | *Patra pinda sweda* | | | vs. | *Upanaha sweda* | | | 0.121 [-0.576 0.818] | 0.734 |
| | 1.93 | 0.46 | 15 | | 2.0 | 0.65 | 15 | | |
| | *Patra pinda sweda* | | | vs. | *Matra basti + patra pinda sweda* | | | 2.139 [1.257 3.02] | 2.00E-06 |
| | 1.93 | 0.258 | 15 | | 3.4 | 0.91 | 15 | | |
| ***iAF*** | *Rasana panchaka kashaya* | | | vs. | *Matra basti + rasana panchaka kashaya* | | | 0.417 [-0.197 1.031] | 0.183 |
| | 0.95 | 0.69 | 20 | | 1.25 | 0.72 | 20 | | |
| | *Samandravya* | | | vs. | *Samanadravya + janu basti* | | | 0.643 [-0.072 1.358] | 0.078 |
| | 2.4 | 0.59 | 15 | | 2.8 | 0.72 | 15 | | |
| ***Blood letting*** | *Janu vestana* | | | vs. | *Jaluakavacharana* | | | 1.855 [1.260 2.439] | 7.82E-10 |
| | 2.39 | 1.359 | 31 | | 4.19 | 1.815 | 31 | | |
| ***nAF*** | *Grihadhumadi + Upanaha Sweda* | | | vs. | *Kottamchukkadi + Upanaha Sweda* | | | 0.799 [0.167 1.432] | 0.013 |
| | 1.0 | 0.51 | 20 | | 1.4 | 0.47 | 20 | | |
| ***Multi-modal treatment*** | *Multi-modal conventional care* | | | vs. | *Multi-modal ayurveda care* | | | 0.64 [0.32 0.97] | <0.001 |
| | 6.7 | [4.4; 8.9] | 74 | | 12.8 | [10.8; 14.8] | 77 | | |

SD=standard deviation; CI=Confidence Interval; N=sample size; iAF: identical ayurvedic formulation; nAF: non-identical ayurvedic formulation; CI within []

**Table 5: Effect Size Estimation: Stiffness**

| | Mean | SD | N | | Mean | SD/95% CI | N | SMD, 95% CI | P-value |
|---|---|---|---|---|---|---|---|---|---|
| **Sudation** | *Patra pinda sweda* | | | vs. | *Matra basti + patra pinda sweda* | | | | |
| | 2.2 | 1.082 | 15 | | 4.06 | 1.1 | 15 | 2.239 [1.341 3.137] | 1.01E-06 |
| **iAF** | *Samanyadravya* | | | vs. | *Janu basti + samanyadravya* | | | | |
| | 2.47 | 0.74 | 15 | | 2.9 | 0.7 | 15 | 0.581 [-0.131 1.292] | 0.11 |
| **Blood Letting** | *Janu vestana* | | | vs. | *Jaluakavacharana* | | | | |
| | 0.903 | 0.98 | 31 | | 1.58 | 1.025 | 31 | 0.668 [0.166 1.173] | 0.0096 |
| **nAF** | *Grihadhumadi + Upanaha Sweda* | | | vs. | *Kottamchukkadi + Upanaha Sweda* | | | | |
| | 1.35 | 0.31 | 20 | | 1.45 | 0.37 | 20 | 0.287 [-0.324 0.898] | 0.357 |
| **Multi-modal treatment** | *Multi-modal conventional care* | | | | *Multi-modal ayurveda care* | | | | |
| | 3.4 | [2.3; 4.4] | 74 | | 6.2 | [5.2; 7.2] | 77 | 0.63 [0.30 0.95] | <0.001 |

SD=standard deviation; CI=Confidence Interval; N=sample size; iAF: identical ayurvedic formulation; nAF: non-identical ayurvedic formulation; CI within bracket.

## Discussion

The present study has identified ten RCoTs under double-arm randomized design using *panchakarma*-based therapies in KOA either as single intervention, in dual combination or within multimodal ayurvedic care. The trial using *panchakarma*-based manual therapies within a multimodal Ayurvedic treatment was the only trial identified to be compared against a standard multimodal Western conventional care. The remaining RCoTs mostly compared a specific *panchakarma*-based treatment with either a different type of *panchakarma*-based treatment or ayurvedic formulation combined with the same *panchakarma*-based treatment, or ayurvedic formulation with and without a *panchakarma*-based treatment. Efficacies of *panchakarma*-based therapies were tested in combination with differing medicines. The outcomes of the trials were compared in the included RCoTs between pre- and post-treatment, and between treatments. The outcomes were measured based on clinical evaluation and subjective reporting on pain, stiffness, swelling, crepitus, range of motion. The multimodal ayurvedic care showed convincing evidence of a better recovery from KOA pain and stiffness after a 12-week treatment in comparison to conventional multimodal care (21). Although not mentioned specifically by the authors about the ayurvedic manual therapies implemented in the multimodal ayurvedic approach, it is sure that these manual therapies were the *panchakarma*-based treatment components for joint disease mentioned in ancient Ayurvedic literatures (10,11,12). Groups receiving these therapeutic cares have reported improvement from treatment than their pre-treatment level in other trials where different therapeutic combinations were compared.

Ayurveda diagnosis on pathological manifestation in the bones and joints in different *vata* related disorders mainly recommends *snehana*, *swedana*, *basti*, *virechana* to either reduce accumulation of excessive *vata* to normal or forceful expulsion from the body (45). *Swedana* was found as frequently practiced treatment in KOA. *Swedana* is mentioned in the preparatory phase of *panchakarma*, though some of the included trials applied *swedana* as a main procedure. According to Ayurvedic scriptures, there are four kinds of *swedana*, which are *tapa* (fomentation), *Upanaha* (warm poultice), *usma* (warm steam) and *drava* (pouring warm liquid) which aims to eliminate toxins by triggering sweating (46). *Upanaha* (warm poultice) was applied in the affected joints in KOA patients to relieve arthritic joint stiffness, heaviness, coldness by therapeutic induction of sweat to remove toxins and freeing circulation in the joints and relaxing muscles. It is assumed that the oil used in *upanaha* establishes lipoidal bond suitable for drug delivery and thereby reducing pain and inflammation, triggers hyperthermia induced improvement of local blood and lymphatic circulation and local tissue metabolism (46). The medicated formulation used with *upanaha* are usually alkaloids, terpenoids, gingerol, tannins and saponins. Another type of fomentation-based sudation using bolus of oil-roasted leaves of medicinal plants (*patra pinda sweda*) was also applied in KOA patients and compared to *swedana* with *upanaha*. Leaves of *Vitex negundo* is one of the primary constituents of *pinda sweda* known to reduce pain & stiffness due to its anti-inflammatory, anti-arthritic properties (47). A therapy common in KOA applying oleation and sudation together known as *janu basti* is also routine in some conditions. Ancient ayurvedic texts recommends treatments based on oleation and sudation as the first line of treatment in KOA. The efficacies of these manual therapies were tested with medicinal formulations. *Janu basti* with orally taken medicines for Ayurvedic palliative care in KOA patients was compared with the medicine intake itself. *Upanaha sweda* with *grihadhumadi* was more effective in KOA treatment than *kottamchukadi* [48]. Efficacy of *upanaha sweda* with *guggulu,* an ayurvedic formulation made from gum resins of *Commiphora sp. and Boswellia sp.* was claimed to be better than the *upanaha sweda. Guggulu* possesses pronounced anti-inflammatory and analgesic property and is a common choice in treating arthritic disease (20). The ayurvedic formulation used in the trials involving sudation has antiarthritic, analgesic, anti-inflammatory compounds extracted from *Pluchea lanceolata, Tinospora cordifolia, Ricinus communis, Withania somnifera, Asparagus racemosus and Glycyrrhiza glabra.*

Interestingly another study reported a better effect of glucosamine sulphate, a conventional drug for osteoarthritis with *janu basti* than with an ayurvedic formulation *(asthishrinkhala)* and *janu basti* combined.

Basti (enema) was found to be another popular choice of treatment in KOA and in severe cases regarded as the most suited therapy. Matra basti (enema with unctuous medication) is a type of Charaka's anuvasana basti used in 2 included trials. *Basti karma* induces s*amshodhana* (bio-purification) and comes under the main procedure of *panchakarma* (Fig.1). In *matra basti* medicated oils with herbicide pastes or oils are introduced into the large intestines through the rectal, urethral passage. They are absorbed into the circulation and opening up channels for the elimination of waste responsible for aggravated *vata* in KOA. In two separate trials *matra basti* was tested with sudation and with ayurvedic medicinal formulation. *Patra pinda sweda* (sudation with oil-roasted medicinal leaves) along with *matra basti* reported better management of KOA. *Withania somnifera* oil used with *matra basti* possesses analgesics as well as anti-inflammatory drug. *Enema* tested with ayurvedic formulation was reported to be more effective in KOA treatment.

One RCoT has reported significant improvement from leech therapy in affected joints in KOA patients. Usually, bloodletting by using leech during aggravation of *vata* in the joints was not mentioned in the ancient Ayurvedic texts, although *Ashtanga Hrydium* has mentioned *asra visruti* (bloodletting) as one of the five main purification therapies. Jaloka Avacharana (leech therapy) is categorized as a non-surgical bloodletting procedure implemented in disease where the blood is vitiated by *raktaja roga* (toxins). Conditions where leech therapy is frequently used as treatment of choice in ayurveda are psoriasis, eczema, melanosis, rheumatoid arthritis, metabolic disorders. The present review found bloodletting using leech as an effective treatment in KOA.

The review has included only randomized comparative trials. Randomized comparative trials may be appropriate to find potentiality of panchakarma-based therapies under comparison in diseases which are not critical in nature and life threatening. The question of using randomized comparative or control design is also debatable due to the holistic and personalized nature of the ayurvedic medicinal system. Certain pathological conditions may also require rescue medication, dosage modification, dietary adjustments during treatment, and occasionally can need longer time for the getting substantial benefit from the treatment. These factors raise concerns about finding the suitability of Ayurvedic treatment under randomized control design. But for the diseases of chronic nature such as KOA and existing anecdotal evidences of benefits from panchakarma-based therapies, RCoTs can be convenient to compare several objectives such as investigating maximum efficacy between particular therapies or combinatorial therapies belonging to panchakarma-based purification, ayurvedic palliative care or with a conventional western treatment. The treatment efficacies can be estimated from the remission of symptomatic outcomes of the diseases. An example is a systematic review which showed studies using ayurvedic herbal preparations as single interventions mostly were conducted under randomized control designs.

Due to the lesser availability of trials for same treatment comparisons, the meta-analysis could not be conducted. Although effect size estimation of pain and stiffness outcome of these trials indicated that mostly differential combination of treatment where a panchakarma-based therapy is common showed significant improvement (Table 4 and 5). But more evidence based on identical type of intervention studies need to be done to acquire a statistically validated comprehensive nature of the therapies.

Besides treatment efficacy, it is essential to emphasize on the treatment related safety concerns under standard guidelines and protocols. Reports of adverse events involved in ayurvedic intervention trials are not uncommon. One of the trials reported safety concerns related to the locomotor system, the skin or to other reasons in the patients under multimodal Ayurvedic care as well as in the multimodal conventional care patients (21). It was also indicated that none of the intervention-related adverse events had led to clinically relevant disease or required hospital treatment. Other 2 RCoTs also reported safety to clinical administration and treatment with medicinal formulations (36,38). No untoward incidents or treatment related side effects were found in these two trials. The trial using leech therapy had few complaints of itching on the site of leech bite during leech therapy, which was subsided by application of turmeric powder (38). This trial had also a total of 6 dropouts from both interventions and the cause was unreported.

The overall conduct of clinical trials, risk of bias was systematically analysed and judged under the reporting guidelines of CONSORT (48). There were some issues on lack of details of randomization method inducted, detailed reporting of dropouts. Except one trial using multimodal ayurvedic care, the remaining trials are not entirely free from bias despite significant and promising treatment outcomes.

One limitation of the review is that the studies were retrieved from the indexed and popular database on published literatures and did not consider the unpublished work available in the form of thesis and dissertations in KOA treatment with Ayurveda. Another limitation was not taking into consideration randomized cross-over, cluster randomized and non-randomized studies designs. These two inclusions might have increased the number of similar trials into systematic analysis.

## Conclusion

Earlier a systematic review was conducted on randomized control, randomized cross-over, cluster randomized and non-randomized studies with pharmacological and non-pharmacological intervention of *Ayurveda* and was the first meta-analysis available on Ayurvedic interventions for OA (16). In comparison, the present systematic analysis has taken into account

specifically the effectiveness of *panchakarma*-based therapeutic treatment as recommended for KOA in ancient Ayurvedic literatures. *Panchakarma*-based therapies mainly founded on *samshodhana* (purification), a concept in Ayurveda targeting elimination of the disease-causing toxins and establishing homeostasis. It is also essential for palliative care used to rehabilitate and rejuvenate the body (26). Thus, emphasis in this area of research will be vital both for the disease prevention and management.

Diagnosis in Ayurveda inspects both the pathological symptoms as well as the psychosomatic nature of the patient. The later depends on the foundation of tri *doshas* (three Ayurvedic functional principles), mainly the concept of movement kinetics (*vata*), anabolism (*kapha*), and metabolism (*pitta*). The differential composition of the three functional principles induces variation of pathological manifestation and is a decisive factor for the treatment choice. The choice of *panchakarma*-based therapies for KOA remains decisive in a highly personalized Ayurveda multimodal care. Thus, comparative testing of different *panchakarma*-based techniques is essential in deciding their inclusion and fitting in an individualized ayurvedic multimodal care. We think that a stratified randomized comparative designs treatment outcome will be viable to check the outcome as KOA is one of the few classical diseases that can be better correlated with the diagnostic principles of Ayurveda. The significance of these type of studies may categorically compare the individual treatment types on the outcome on pain and stiffness in KOA. The trials comparing the single interventions with the combinations of the interventions are important to weigh the efficiency of a treatment component in a multi care design. Future study designs should also consider long-term observations made at Ayurveda-Arthritis treatment and advanced research centre referring to benefits of Ayurveda in KOA.

**Statement of Ethics**

An ethics statement is not applicable because this study is based exclusively on avalibale published literature.

**Conflict of Interest Statement:**

The authors declare that there is no conflict of interests regarding the publication of this article.

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