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Authors: Jie Kie Phang, Yu Heng Kwan, Hendra Goh, Victoria Ie Ching Tan, Julian Thumboo, Truls Østbye, Warren Fong

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**Title:**

Complementary and alternative medicine for rheumatic diseases: A systematic review of randomized controlled trials

**Author's name and affiliations:**

Jie Kie PHANG[1,2]*, Yu Heng KWAN[1]*, Hendra GOH[3]*, Victoria Ie Ching TAN[4], Julian THUMBOO[1,2], Truls ØSTBYE[1], Warren FONG[2,5,6]

[1]Program in Health Systems and Services Research, Duke-NUS Medical School, Singapore

[2]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore

[3] Faculty of Science, National University of Singapore, Singapore

[4] Faculty of Medicine, University of Queensland

[5] Duke-NUS Medical School, Singapore

[6]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

*Co-first authors

**Corresponding author's detail:**

Corresponding author:

Mr. Yu Heng KWAN, BSc (Pharm)(Hons)

MD-PhD Candidate

Duke-NUS Graduate Medical School

8 College Road

Singapore 169857

Email: yuheng@u.duke.nus.edu

**Condensed Running Title:** CAM, rheumatic diseases

Highlight

- We identified 60 good quality RCTs using CAM as intervention for patients with rheumatic diseases. Treatment modalities include acupuncture, Ayurvedic treatment, homeopathic treatment, electricity, natural products, megavitamin therapies, chiropractic or osteopathic manipulation, and energy healing therapy.
- Evidence indicates that some CAM therapies may be useful for rheumatic diseases, such as acupuncture for osteoarthritis.
- There were only minor adverse reactions observed for CAM interventions presented.

**ABSTRACT**

Objectives:

To summarize all good quality randomized controlled trials (RCTs) using complementary and alternative medicine (CAM) interventions in patients with rheumatic diseases.

Methods:

A systematic literature review guided by the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) was performed. We excluded non–English language articles and abstract-only publications. Due to the large number of RCTs identified, we only include "good quality" RCTs with Jadad score of five.

Results:

We identified 60 good quality RCTs using CAM as intervention for patients with rheumatic diseases: acupuncture (9), Ayurvedic treatment (3), homeopathic treatment (3), electricity (2), natural products (31), megavitamin therapies (8), chiropractic or osteopathic manipulation (3), and energy healing therapy (1). The studies do not seem to suggest a particular type of CAM is effective for all types for rheumatic diseases. However, some CAM interventions appear to be more effective for certain types of rheumatic diseases. Acupuncture appears to be beneficial for osteoarthritis but not rheumatoid arthritis. For the other therapeutic modalities, the evidence base either contains too few trials or contains trials with

contradictory findings which preclude any definitive summary. There were only minor adverse reactions observed for CAM interventions presented.

Conclusion:

We identified 60 good quality RCTs which were heterogenous in terms of interventions, disease, measures used to assess outcomes, and efficacy of CAM interventions. Evidence indicates that some CAM therapies may be useful for rheumatic diseases, such as acupuncture for osteoarthritis. Further research with larger sample size is required for more conclusive evidence regarding efficacy of CAM interventions.

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**Introduction**

Rheumatic diseases encompass a broad spectrum of musculoskeletal, arthritic and connective tissue disorders, including rheumatoid arthritis (RA), osteoarthritis (OA), fibromyalgia, gout, vasculitides, systemic sclerosis, systemic lupus erythematosus (SLE), ankylosing spondylitis and psoriatic arthritis [1]. Rheumatic diseases are associated with reduced productivity, significant disability and lowered quality of life [2]. Conventional therapies for rheumatic diseases include nonsteroidal anti- inflammatory drugs (NSAIDs), disease- modifying anti- rheumatic drugs (DMARDs) and biologics [3]. However, some patients do not respond well to these conventional therapies [4]. Thus, patients with rheumatic diseases often seek other forms of treatments such as complementary and alternative medicine (CAM) [5].

The World Health Organization has defined CAM as 'A broad set of healthcare practices that are not part of the country's own tradition and are not integrated into the dominant healthcare system' [6]. CAM covers a spectrum of approaches that may prevent or treat diseases. CAM practices may be systematically divided into five main categories: alternative medical systems (for example homeopathy and acupuncture), biologically based therapies (for example herbal products, dietary constituents or additives that are fund in nature), manipulative and body- based therapies (for example massage, chiropractic and osteopathic manipulation), mind- body therapies (for example meditation, hypnosis, cognitive therapy, patient support groups and prayer) and energy healing therapies (for example Qi gong, reiki and therapeutic touch methods) [7]. Previous studies indicated that 60% to 90% of patients with rheumatic diseases have used some form of CAM [5, 8]. Rheumatological conditions are also among the commonest disease conditions encountered by CAM practitioners [9].

The underlying mechanisms for the efficacy of CAM have not been elucidated fully. It has been hypothesized that acupuncture may block the pain pathways by releasing encephalin [10]; *Tripterygium wilfordii* (also known as Thunder God Vine) [10], rose-hip [11], andrographolide (extracted from *Andrographis paniculata*) [12], *Nigella sativa* oil capsules [13], GCSB-5 (a traditional medicine preparation) [14], *Ganoderma lucidum* (more commonly known as Ling Zhi) when combined with San Miao San (a herbal remedy used empirically to treat arthritis) [15], Avocado–soybean unsaponifiable—Expanscience (ASU-E) [16], chondroitin [17], glucosamine sulfate [17], alpha-linolenic acid [18], gammalinolenic acid (found in borage seed oil) [19], willow bark [20], antioxidant vitamins such as Vitamin C and Vitamin E [10], and electroacupuncture [10], may help to lower the level of pro-inflammatory cytokine; Carnitine [21] and Aflapin® [22] may have anti-inflammatory properties by exerting its effects on lipid peroxidation and matrix metalloproteinase respectively. Dehydroepiandrosterone (DHEA) and Vitamin D may help to alleviate symptoms of rheumatic diseases

through its immunoregulatory properties [23, 24]. Plant- derived polysaccharides may be important to modulate the gastrointestinal microbial [25], when may be important in pathogenesis of rheumatic diseases [26]. Vitamin K may be important for bone metabolism [27]. The mechanism of homeopathy and Ayurvedic medicine is less clear, but there is some evidence suggesting that their antioxidant properties may be responsible to alleviate the symptoms of rheumatic diseases [28, 29]. Similarly, the mechanism of electrical stimulation is still speculative, though it is generally believed that the effects are primarily mediated through direct actions on the brain [30]. It has been proposed that manual therapy can act on the central pain pathways [31]. There is no clearly mechanism of action for magnets, although it might involve reduction of inflammation [32]. The growing interest in CAM among patients with rheumatic diseases clearly indicates the need for a more thorough investigation of both the efficacy and safety of CAM.

Currently, there is a large number of studies evaluating different forms of CAM for rheumatic patients with rheumatic diseases [33, 34]. However, there has been no systematic review with clear quality assessment encompassing various categories of CAM used in patients with rheumatic diseases. Therefore, we aimed to conduct a systematic review including all randomized controlled trials (RCTs) using some form of CAM intervention in patients with rheumatic diseases.

**Methods**

*Search strategy*

We identified potentially relevant articles using PubMed® and Embase® searches. Literature review start date was unrestricted and was current as of May 2017. A search strategy (Supplemental Table 2) of three components was used: (1) disease terms (2) keywords of the CAM and (3) randomized controlled trials. The disease terms were adapted from a previously published paper regarding rheumatic diseases [35]. Keywords of CAM interventions include the treatments listed in the 2002 and 2007 NCCAM report regarding prevalence of CAM in United States [7, 36]. We also reviewed reference lists and searched previous reviews on similar topics.

*Inclusion criteria*

Two authors (JKP and HG) independently screened the titles of selected articles and excluded duplicates and those obviously irrelevant. Two authors reviewed abstracts and full-text articles against prespecified eligibility criteria. We included RCTs of CAM conducted among patients with rheumatic diseases. We excluded non–English language articles and abstract-only publications. The references of all selected

relevant articles were manually searched to obtain additional relevant publications. Any disagreement was resolved by discussion to reach consensus.

*Data extraction and Quality Assessment*

One investigator (JKP) extracted study data, and a second (HG) verified the accuracy of the extractions. The data items extracted were: sample size, age, disease, experimental design, characteristics of the intervention in all trial arms including type and dose of therapy, primary and secondary outcome measures, findings and side effects. Two investigators independently assessed the quality of each study using the Jadad scoring system [37]. The Jadad scale is a scoring system that has three items adding up to a maximum score of 5. Zero, one, or two points can be given for randomization and double-blinding; zero or one point for the description of drop-outs and withdrawals. It should be noted that for Jadad scoring system, double blinding was considered appropriate if it was stated or implied that neither the evaluator nor the subject could identify the intervention being assessed [37]. The Jadad scoring system is relatively straightforward to apply and was chosen because it has been shown to present the best validity and reliability evidence for assessment of methodological quality of RCTs [38]. Given the large number of RCTs of CAM among patients with rheumatic diseases, only RCTs with a Jadad score of five were included in the review. Risk of bias was assessed using Jadad scoring.

*Data presentation*

We presented primary outcome measures, findings, comments and adverse events for each trial, categorized by the type of therapy, to allow readers to understand the benefit and risk associated with each therapy. We also present the control used in each study. For this review, placebos are defined as inactive substances used to compare results with active substances while sham treatments refer to false treatments for procedures. Secondary outcomes and measures can be found in supplementary data.

**Results**

As shown in Figure 1, we identified 5,472 records from our searches in Embase® and Pubmed®. After removing 798 duplicates, 4674 articles remained. Of these, 501 articles were deemed relevant after title and abstract screening. Of the 501 articles, 441 articles did not meet the inclusion criteria as JADAD score was less than 5. A total of 60 articles met the inclusion criteria. We did not identify any additional articles from hand-searching.

Our literature search has identified 60 good quality RCTs using CAM as intervention for patients with rheumatic diseases: 9 RCTs for acupuncture, 3 concerning Ayurvedic treatment, 3 RCTs for homeopathic treatment, 2 RCTs using electricity, 31 RCTs examining nonvitamin, nonmineral, natural products, 8 assessing megavitamin therapies, 3 RCTs looking at chiropractic or osteopathic manipulation, and 1 RCT examining energy healing therapy (Table 1).

*Acupuncture*

We have identified nine high quality RCTs concerning acupuncture for patients with rheumatic diseases. Six RCTs reported no statistically significant difference between experimental and control groups [39-44], while the remaining three RCTs showed that acupuncture had beneficial effects for patients with rheumatic diseases, especially knee OA [45-47]. For RA, the evidence seems to be clearly negative with all three available RCTs demonstrating no beneficial effects [40-42]. A wide range of acupuncture treatment protocol was used, with different frequency of treatment, length of treatment, number of acupuncture points and usage of electric current. In addition, the sham or placebo treatments used in the studies were heterogenous, with some using real acupuncture points but with no skin penetration [39, 40], superficial acupuncture at non- acupuncture points [41], or needle quickly withdrawn after skin puncture [42]. There were also different modalities of acupuncture treatment, including traditional acupuncture without electricity [40, 41, 44, 46], laser acupuncture [45], dry needling [39], gold bead implantation [43], electroacupuncture [42], and moxibustion [47]. Gold bead implantation at acupuncture points did not result in any significant differences in pain, stiffness and function among patients with knee OA [43]. Moxibustion, is a non-invasive procedure that involves burning moxa, the herb Artemisia vulgaris, at acupuncture points [48]. Among patients with knee OA, moxibustion treatment appeared to improve function and pain score [47]. Similarly, laser acupuncture appeared to be beneficial for patients with knee OA [45]. Dry needling, which involves placing needles at trigger points, was found to lower pain among patients with myofascial pain syndrome [39].

*Ayurveda*

The three RCTs investigating Ayurvedic medicine (classical Hindu medical tradition) in patients with RA (N=1) and knee OA (N=2) did not show statistically significant between- group differences in the outcomes evaluated [49-51].

*Homeopathic treatment*

We have identified three high quality RCTs on homeopathic treatment, which is a treatment developed by Samuel Hahnemann [52]. Homeopathy uses preparations of substances whose effects when

administered to healthy subjects correspond to the manifestations of the disorder in the individual patient [52]. Only one high quality RCT investigating homeopathy showed significantly greater improvements in primary outcomes evaluated including tender point count ($p<0.05$) and tender point pain ($p<0.01$), quality of life ($p<0.05$) and global health ($p < 0.05$) for patients with fibromyalgia (FM) [53], while the other RCTs concluded that homeopathic treatment appeared to have no beneficial effects for RA and knee OA [54, 55]. There were two good quality RCTs investigating the use of electricity on FM and RA. However, conflicting results exist as electrical stimulation appeared to be beneficial for FM but not RA [56, 57].

*Nonvitamin, nonmineral, natural products*

Among the thirty one RCTs concerning nonvitamin, nonmineral, natural products, most of them investigated patients with RA (N=11, 34%) and OA (N=15, 47%). There were only five high quality RCT investigating the effect of natural products on rheumatic diseases other than RA and OA: one article each on DHEA for FM [58], one investigated Traditional Chinese medicine (TCM) for Sjögren's syndrome [59], one investigated Chuanhu anti-gout mixture [60], one investigated TCM for SLE [61] and one on TCM for IBS-C [62]. Twenty one out of the twenty nine RCTs concerning nonvitamin, nonmineral, natural products included placebo control. Fourteen placebo-controlled studies on nonvitamin, nonmineral, natural products showed beneficial effects of CAM on rheumatic diseases: ShengJinRunZaoYangXue for Sjögren's syndrome [59], Chinese Herbal medicine for IBS-C [62], Tong Luo Hua Shi capsules for RA [63], Rose-hip for RA [64], Mahame-Mafasel pomade for knee OA [65], Aflapin for knee OA [66], 4Jointz cream for knee OA [67], topical *Tripterygium wilfordii* for RA [68], oral GCSB-5 for hand OA [69], rose-hip for knee and hip OA [70], willow bark extract for knee and hip OA [71], methylsulfonylmethane (MSM) for knee OA [72], L-carnitine for knee OA [73] and topical glucosamine and chondroitin preparation for knee OA [74]. Placebo- controlled studies investigating Ambrotose Complex containing dietary plant- derived polysaccharides for RA [75], *Ganoderma lucidum* (Ling Zhi) and San Miao San for RA [76], Andrographolides, which is extracted from *Andrographis paniculata*, for RA [77], *Nigella sativa* oil capsules for RA [78], Alpha-linolenic acid for RA [79], Huo-Luo-Xiao-Ling capsules for knee OA [80], and ASU-E for hip OA [16], failed to show beneficial effects. A study demonstrated that change in steroid dose was not significantly different between patients with SLE who received 100% Dan-Chi-Liu-Wei combination, a traditional Chinese medicine (TCM), and those who received only 10% TCM [61].

Though topical glucosamine and chondroitin preparation may have beneficial effects for knee OA [74], interestingly, there were another that looked at the orally administered glucosamine, but did not find evidence supporting the efficacy of glucosamine. Overall, the two studies constituted conflicting evidence for that glucosamine is effective for knee OA [74, 81]. Another study comparing reparagen, a dietary

supplement derived from South American botanicals, and glucosamine found that both produced substantial improvements in pain [82].

Five studies on nonvitamin, nonmineral, natural products were non-inferiority studies- one study showed that SKI306X, which consists of biologically active ingredients from three plants, was not inferior to celecoxib for patients with RA [83], another study showed that Chuanhu anti-gout mixture, a TCM, was not inferior to colchicine [60]; a study demonstrated that GCSB-5 is comparable to Celecoxib in terms of the efficacy and safety for treatment of OA of knee joint [84]; another study demonstrated that treatment with MD-Knee was not inferior of the treatment with SUPARTZ® (sodium hyaluronate), with a confidence level higher than 99% [85]; another study could not confirm the premise of combination of borage and fish oils would be superior to either oil alone [86].

In a study looking at orally administered *T. wilfordii* based therapy [87], RA patients were classified into predictor positive (P1) and predictor negative (P2) group, and were randomly assigned to accept the *T. wilfordii* based therapy and Methotrexate and Sulfasalazine combination therapy (M&S) for 24 weeks, respectively. The ACR 20 responses were 82.61% in TwHF/P1 group, significantly higher than that in TwHF/P2 group and in M&S/P1 group but not higher than in M&S/P2 group.

*Megavitamin therapy*

There were two high quality RCTs investigating the effect of Vitamin D supplementation on knee OA [88, 89]. However, conflicting evidence exists concerning the supplementation of vitamin D in knee OA condition. Lastly, Vitamin E, and magnesium-, calcium-rich supplement appeared to have no beneficial effects for patients with knee OA [90, 91]. One study has found that Vitamin D supplementation improved the disease activity of juvenile SLE, though it should be noted that the sample size of the study might be small with only forty patients in total [92]. It was also found that Vitamin K supplementation at 10 mg/day for 8 weeks did not alter joint destruction and immune status in the patients with RA compared with the controls [93]. A pilot, small- sample study among thirty four adults with fibromyalgia syndrome failed to show efficacy of Myers' Cocktail, a solution containing Vitamin B and C [94]. However, calcium supplementation improved the total body bone mineral density among young adults with RA [95].

*Chiropractic or osteopathic manipulation*

We identified three studies examining chiropractic or osteopathic manipulation. Two of the studies were from the same group and both reported beneficial effects of manual treatment including mobilization for specific subtypes of rheumatic diseases - Carpometacarpal joint OA and Thumb carpometacarpal OA [96, 97].

Kinesio taping, which involves placing elastic adhesive material, appeared to have no beneficial effects for RA [98].

*Energy healing therapies*

There was only one high quality RCT investigating magnetic bracelet and no beneficial effects was reported [99].

**Discussion**

The studies presented in this systemic review were heterogenous in terms of interventions, disease, measures used to assess outcomes, and efficacy of CAM interventions. The studies do not seem to suggest a particular type of CAM is effective for all types for rheumatic diseases. However, some CAM interventions appear to be more effective for certain types of rheumatic diseases, such as acupuncture for OA. Most of the high quality RCTs focused on osteoarthritis (N=30, 50%), possibly because currently OA has no effective therapy [100]. Therefore, the treatment of OA is primarily focused on managing the condition by minimizing morbidity and maximizing quality of life [101], and there is growing interest for patients with knee OA to seek CAM such as acupuncture, glucosamine and vitamin D supplementation to alleviate arthritic symptoms [102, 103]. Relatively clear consensus exists that acupuncture is effective for OA, especially knee OA, which can be seen in this systematic review as well as previous systematic review [104]. However, only a moderate effect of glucosamine has been demonstrated for knee OA, which is in agreement with the conclusion of previous systematic review [105]. Our systematic review also found that there is conflicting evidence regarding the use of vitamin D supplementation for knee OA, which also is in agreement with previous systematic review [106]. For the other therapeutic modalities, the evidence base either contains too few trials or contains trials with contradictory findings which preclude any definitive summary.

We identified eighteen good quality RCTs assessing CAM interventions among patients with RA. For RA, the good quality RCTs failed to show specific effects of acupuncture for patients, which is in agreement with previous systematic review [107]. Among the nonvitamin, nonmineral, natural products investigated, only *Tripterygium wilfordii* and Tong Luo Hua Shi have beneficial effects on the symptoms of RA [63, 68, 87].

For fibromyalgia, there was some evidence regarding the efficacy of homeopathic treatment and cranial electrical stimulation in decreasing pain. For Sjögren's syndrome, there was one trial demonstrating the efficacy of ShengJinRunZaoYangXue granules. Another trial showed that Chinese Herbal Medicine capsule

can significantly improve the global symptom improvement of patients with constipation-predominant irritable bowel syndrome.

The CAM interventions in this review had minor or no side effects reported. Notable adverse reactions were observed in patients treated with a particular Ayurvedic formulation which might be associated with elevated serum glutamic pyruvic transaminase (SGPT) level [51], *Tripterygium wilfordii* (also known as Thunder God Vine) supplementation tends to be associated with diarrhea, frequent withdrawal form therapy, nausea, dyspepsia, abdominal pain, male infertility, dysmenorrhea [87], androgenic side effects associated with DHEA supplementation [58], and possible hypercalcemia from vitamin D supplementation [88].

There were some limitations to this review. Due to the large number of interventions, reviewing all primary literature was not feasible. We only included higher-quality RCT with Jadad score of 5 that were most relevant to the review scope. The Jadad scoring system was chosen because it has been shown to present the best validity and reliability evidence for assessment of methodological quality of RCTs [38]. Studies are scored according to the presence of three key methodological features of clinical trials, specifically randomization, double-blinding, and accountability of all patients [108]. It has been suggested that heightened placebo effects are especially prominent in trials concerning CAM, highlighting the need for randomization and double-blinding [109]. However, some CAM treatment approaches such as spa and yoga do not have obvious suitable double- blinded control. For such CAM interventions, Jadad scoring system may not be suitable. However, as the aim of this systematic review is to summarize the available good quality RCTs involving CAM interventions for patients with rheumatic diseases, it was necessary to conduct quality assessments of the RCTs. Among the common trial quality assessment tools, only Jadad scoring system does not require the care provider or those administering the intervention to be blinded to treatment allocation [108]. This allows evaluator- and subject- blinded RCTs, which are common in invasive interventions such as acupuncture [39-41], to be included in the analysis. Moreover, conventional therapies such as analgesia and physiotherapy may confound the results of the trials. However, as the reporting of the use of conventional therapies is not clear in the studies included, we could not assess the impact of the conventional therapies on the results of the trials. Future research should provide more insight in this area. In addition, we excluded non–English-language articles which may contain relevant studies on CAM widely practised in non- Western culture. Moreover, the existence of publication bias in research may lead to an overestimate of treatment efficacy of CAM interventions [110]. Limitations also existed in the evidence base. For each CAM intervention, trials were heterogeneous in terms of study design. Different

dosage, number of treatment sessions, duration, frequency of sessions, methods of assessing outcomes and efficacy, and statistical analysis were employed for each study, making it difficult to compare results across studies. Therefore, standardization in CAM treatment modality in trials may be useful to elucidate the efficacy of the various CAM treatment modalities.

In conclusion, we identified 60 good quality RCTs which were heterogenous in terms of interventions, disease, measures used to assess outcomes, and efficacy of CAM interventions. Several CAM interventions are associated with beneficial effects for patients with rheumatic diseases. Relatively clear consensus exists that acupuncture is effective for OA, especially knee OA. Only *Tripterygium wilfordii* and Tong Luo Hua Shi have beneficial effects on the symptoms of RA, while all the other CAM interventions are equivocal or of no benefit. Further research in CAM interventions should focus on good quality trials with larger sample size before progressing to pragmatic trials to evaluate the effectiveness of the CAM interventions.

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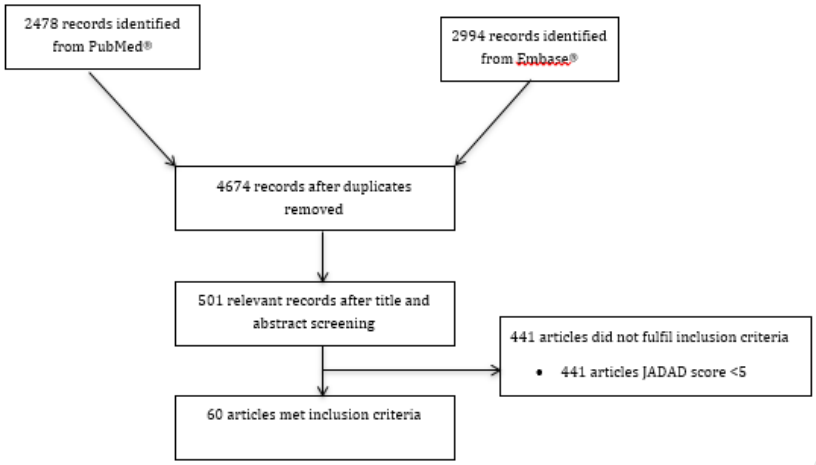


**Figure 1.** Flow chart on selection of articles for review

**Table 1**: Characteristics of good quality trials of complementary and alternative medicine as defined by NCCAM in patients with rheumatic diseases

| Ref | N; mean age (years) | Disease | Intervention (name; dosage or frequency; duration) | | | Primary Outcomes Measures | Findings and Comments | Side effects |
|---|---|---|---|---|---|---|---|---|
| | | | Design | Experimental | Control | | | |
| **Acupuncture** | | | | | | | | |
| [39] | 39; 42 | MPS | 1:1 | Dry needling; six sessions; 4 weeks | Blunted needle without penetration of skin | Pain measured using VAS | Pain was ***significantly lower*** in the dry needling group ($p<0.001$). | Not reported |
| [40] | 56; *Mean age not reported* | RA | 1:1 Cross-over | Acupuncture; 5 treatments at weekly interval | Needle introducer held without pressure and no skin penetration | ESP, CRP, VAS p, VAS G, 28 swollen joint count, 28 tender joint count, GHQ and modified DAS index | ***No significant difference*** between two sequence groups except for GHQ anxiety. | No AEs reported |
| [41] | 40; 50 | RA | 1:1 | Acupuncture; Two sessions weekly; 5 weeks | Superficial acupuncture at non-acupuncture points | Proportion of patients who reached ACR20 response | At week 5, there was ***no significant difference*** between intervention groups. | AEs minimal |
| [42] | 36; 58 | RA | 1:1:1 | 1. EA; 2. TCA; Two 40 min sessions weekly; 10 weeks | Needle was quickly withdrawn after puncturing skin to a depth of 2mm | Changes in the pain score at week 10 | At week 10, the pain score remained ***unchanged*** in all 3 groups. | AEs minimal |
| [44] | 213; 60 | Knee OA | 1:1 | Acupuncture; 12 sessions; 6 to 12 weeks | Identical-appearing nonpenetrating Streitberger needles | Change in WOMAC total score from baseline to 12 weeks | ***No significant difference*** between groups in primary outcomes evaluated. | 17 AEs in experimental group and 15 AEs in control group |
| [45] | 55; 53 | Knee OA | 1:1 | Laser acupuncture; 20 min per day and 5 days per week; 10 days | Sham laser therapy, 0 J/cm2 | pVAS, 50-foot walking time, knee circumference, MTS, and WOMAC | ***Statistically significant improvement*** was observed in PVAS, 50 foot w, and KC in experimental group. In control group, | Not reported |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | statistically significant improvement was observed in PVAS, 50 foot w, and WOMAC. | |
| [46] | 570; 65.5 | Knee OA | 1:1:1 | Electroacupuncture; 23 sessions over 26 weeks | 1. Same active needle placement but no skin puncture 2. Educational control | WOMAC function and pain score | ***Greater improvement*** in WOMAC function scores in experimental group (p=0.01), WOMAC function score (p= 0.01), WOMAC pain score (p= 0.003). | 7%, 3% and 4% of participants in acupuncture, sham and educational control group experienced AEs |
| [43] | 40; 68 | Knee OA | 1:1 | Gold bead implantation through needles at acupuncture points | No gold bead implantation after placing needles at acupuncture points | Patient's assessment of knee pain, knee stiffness and knee function as well as physician's rating of knee and knee function | ***No significant difference*** between experimental and control group in all outcomes evaluated (all p-values> 0.05). Differences in the use of analgesics at the beginning and at the end of the study cannot be detected with certainty due to small sample size. | Not reported |
| [47] | 110; 65 | Knee OA | 1:1 | Moxibustion; three times a week; 6 weeks | Sham device with insulated metal membrane which isolates the smoke and heat | WOMAC pain and function scores taken at the end of the 6-week course of treatment | WOMAC pain scores showed ***greater improvement*** in the active treatment group than in control at Week 6 (p<0.001) as did WOMAC physical function scores of the active treatment group at week 6 (p= 0.015). | No significant AEs were found |
| **Ayurveda** | | | | | | | | |
| [49] | 182; 45 | RA | 1:1 | RA-I; 444 mg/day; 16 weeks | Placebo | Reduction of 2 grades or from grade 2 to grade 1 in patient and physician GA; and ACR20 | ***No significant difference*** between groups in primary outcomes evaluated. | No significant differences in the side effects profile between groups |
| [50] | 236; 54 | Knee OA | 1:1:1:1:1:1 | 1. *Shunthi + Guduchi + Gokshur* | 1. Placebo (Maize starch) | Active pain and WOMAC index | ***No significant difference*** ($p < .05$) for pain (weight bearing) and WOMAC | Only Mild AEs were reported. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 2. *Shunthi* + *Guduchi* + *Ashwagandha* + *Gokshur*<br>3. *Shunthi* + *Guduchi* + Amalaki<br>4. *Shunthi* + *Guduchi*<br>5. *Shunthi* + *Guduchi* + *Ashwagandha* | 2. Glucosamine sulphate | | questionnaire (knee function); placebo response was high. | |
| [51] | 418; 55.5 | Knee OA | 1: 1:1: 1 | 1. SGCG Ayurveda formulation<br>2. SGC Ayurveda formulation | 1. Glucosamine<br>2. Celecoxib | Active pain, WOMAC pain and functional score | ***Significant improvement*** was seen in each of the intervention groups. Difference between any two intervention groups for the mean change from baseline to completion for primary efficacy measure was within the equivalence range. | ADR: 29% Seven patients in experimental group were withdrawn and SGPT normalized after stopping the drug. |
| **Homeopathic treatment** | | | | | | | | |
| [53] | 62; 49 | FM | 1:1 | LM; 1/50000 dilution; 4 months | Placebo | McGill Pain Questionnaire, Appraisal of Fibromyalgia QoL scale, global self-rated health scale, and POMS scale | Participants on active treatment showed ***significantly greater improvements*** in tender point count ($p< 0.05$) and tender point pain ($p< 0.01$), quality of life ($p< 0.05$) and global health ($p< 0.05$). | No patient withdraw due to ADR |
| [54] | 56; 64 | RA | 1:1 | 1. Individualized homeopathy prescribed as tablets<br>2. Standardized commercial homeopathic complex | Placebo | ACR20 response and improvement in the patient's GA of health using 100-mm VAS | ***No significant difference*** in all primary outcomes evaluated | 1 SAE in experimental arm |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| [55] | 184; 64 | Knee OA | 1:1 | SRL® gel; 1g of gel three times daily; 4 weeks | Piroxicam gel (Feldene®) | Pain on walking in the previous 24h assessed using VAS, pain on palpation on the affected knee using single-joint Ritchie index | N***o significant difference*** between treatment groups in the single-joint Ritchie index (p=0.78). | 12 AEs in SRL<br>16 AEs in piroxicam |
| **Electricity** | | | | | | | | |
| [56] | 46; 51 | FM | 1:1:1 | Used Alpha-Stim CES device for 60 continuous minutes each day for 8 weeks | 1. Sham<br>2. Usual care alone | Pain ratings 0-10 NRS, Short-Form McGill Pain Questionnaire, Lee's Fatigue Inventory, General Sleep Disturbance Scale, Daily Stress Inventory, FIQ and fMRI | Individuals using the active device had a ***greater decrease in average pain*** (p =0 .023) than individuals using the sham device or receiving usual care alone over time. Individuals using an active CES device had a decrease in activation in the pain processing regions of the brain compared to those using a sham device based on fMRI analyses of 6 participants. | Not reported |
| [57] | 30; 51 | RA | 1:1 | Exposure to EF-HVAC for 20 min/ day; 2 weeks | Sham-apparatus | DAS-CRP | DAS28 score comparison between two groups at 12 weeks after treatment was ***not significant***. | No AEs related to treatment |
| **Nonvitamin, nonmineral, natural products** | | | | | | | | |
| [59] | 240; 48 | Sjögren's syndrome | 2:1 | ShengJinRunZaoYangXue granules; Once daily; 6 weeks | Placebo | Salivary flow rate, Schirmer test results and sugar test result | For Schirmer test, the between-group and within-group before- and after paired comparison results were ***statistically significant*** (p<0.05). . | 4% treatment-related AEs in experimental group vs 0% in control group |
| [58] | 52; 59 | FM | 1:1 | DHEA; 50 mg/day; 1 month | Placebo | Quality of life measured by PGWBI | ***No significant difference*** between treatment and placebo in any of the primary evaluated. | Androgenic side effects were more common with DHEA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| [60] | 176; 52 | Gout | 1:1 | Chuanhu anti-gout Mixture; 250 ml/day: 12 weeks | Colchicine | Recurrence rate of acute gouty arthritis | Chuanhu anti-gout mixture was ***not inferior*** to Colchicine. | Rates of total AEs were 3.27% and 28.41% in CH group and Col group |
| [61] | 46; 36 | SLE | 1:1 | Conventional medicines and 100% TCM (LWDHW and Dan-Chi San) | Conventional medicines and 10% TCM | Steroid dosage after 6 months of combined therapy | Change in steroid dose was ***not statistically significant*** in either group. | No difference in the frequency of AEs between both groups |
| [62] | 125; 48 | IBS-C | 1:1 | Chinese Herbal Medicine capsule; 10/ day; 8 weeks | Placebo | Global symptom improvement | 68% of CHM group and 43% of placebo group ***changed from no relief to adequate relief*** (p = 0.010). | 6 AEs potentially associated with the study drug, |
| [86] | 150; 59.3 | RA | 1:1:1 Non-inferiority | 6 borage seed oil capsules plus 7 sunflower seed oil capsules daily; 18 months | 1. Fish oil and sunflower seed oil capsules 2. Borage seed oil and fish oil capsules | DAS-28 | The premise of combination of borage and fish oils would be superior to either oil alone is ***not confirmed.*** | With fish as the reference group, borage IRR = 1.56 and combined IRR = 2.61 |
| [87] | 192; 47 | RA | 1:1:1:1 | *Tripterygium wilfordii* based therapy 1. GTT; 10 mg 3 times a day; 24 weeks 2. YSJB pill; 8g/each time and 3 times a day; 24 weeks 3. Placebo of MTX and SSZ; 24 weeks | 1. MTX 2. SSZ3 Placebo of GTT and YSJB | ACR20 at week 24 | ***RR value is 1.2791*** in predictor positive group based on ACR 20 response (p = 0.0492). | AE TwHF/P+: 26.9% M&S/P+ : 35.9% TwHF/P−: 25.2% M&S/P−: 25.5% |
| [68] | 61; 41 | RA | 1:1 | Topical *T. wilfordii*; 6 weeks | Placebo | Modified ACR-20 response rate | Modified ACR-20 response rate ***differed significantly*** between topical TW (58%) vs placebo (20%) (p= 0.002). There was an | Not reported |

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| | | | | | | | 8.1-fold increase in the modified ACR20 response for the TW compared to the placebo group. | |
| [75] | 69; 60 | RA | 1:1 | Ambrotose Complex containing dPP; 1.3 g/day; 6 months | Placebo | Changes in the DAS score from baseline to end of treatment | ***No significant difference*** in primary outcomes between the experimental and placebo groups | No AEs reported |
| [63] | 118; 49 | RA | 1:1 | TLHS capsules; 4.8, 3.6, or 2.4 g/day; 8 weeks | Placebo | ACR20 | After 8 weeks, TLHS 4.8 g and 3.6 g groups had ***significantly higher improvement rates*** in ACR20 than in the placebo group (all $p < 0.05$). | ADR 4.8g: 3.4%; 3.6g: 1.7%; 2.4g: 3.4%; Placebo: 1.7% |
| [76] | 65; 28 | RA | 1:1 | *Ganoderma lucidum* and SMS; 4g and 2.4g/day respectively ; 24 weeks | Placebo | Number of patients achieving ACR20 response | ***No significant difference*** in ACR20 response between experimental and control groups. | No reports of SAEs |
| [83] | 183; 52 | RA | 1:1 Double dummy. Non-inferiority | SKI306X; 200 mg/day; 6 weeks | Celecoxib | Change in patient assessment of pain using VAS | SKI306X was ***not inferior*** to celecoxib. | Drug-related AEs: 29.7% patients in the SKI306X group VS 23.9% patients in the celecoxib. |
| [77] | 58; 46 | RA | 1:1 | Andrographolides; 30mg three times a day; 14 weeks | Placebo | Reduction of joints pain, stiffness, VAPS, EULAR and duration of morning stiffness | ***No significant difference*** in intensity of joint pain between the experimental and control groups. | 9 AEs in control group 11 AEs in experimental group |
| [78] | 39; 43 | RA | *1:1* | *Nigella sativa* oil capsules; 1000mg/day;8 weeks | Placebo | Biochemical analysis of blood, measurements of cytokine levels, antioxidant defense and oxidative stress | ***No significant difference*** between two groups at the baseline or end of the study for all other measurements (all $p>0.05$). DAS28 score was significantly lower in the *N. sativa* group as compared with the | No SAE reported |

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| | | | | | | | placebo group at the end of the study *(p-value not reported).* | |
| [64] | 89; 56.6 | RA | 1:1 | Capsulated rose-hip powder; 5g/day; 6 months | Placebo | HAQ- DI at 6-month | Mean change in HAQ-DI of patients in the treatment group ***improved*** whereas in the placebo group it worsened (p=0.014 and p=0.032). | 14 reports on side effects in experimental group and 26 reports in placebo |
| [79] | 65; 37 | RA | 1:1 | ALA; 1200 mg/day; 8 weeks | Placebo | Inflammatory biomarkers including serum hs-CRP, TNF-α, IL-6, and serum MMP-3 as a marker of joint erosion | ***No significant difference*** were observed in serum levels of hs-CRP, TNF-a, IL-6, and MMP-3 within and between the ALA and placebo groups ($p > 0.05$). | No SAEs of treatment was reported |
| [65] | 42; 58.4 | Knee OA | 1:1 | Marhame-Mafasel pomade; 1.5g; every 8 hours over 6 weeks | Placebo | Pain, physical function and stiffness measured by WOMAC | ***Significant difference*** between Marhame-Mafasel and placebo groups for pain, physical function, stiffness and disease severity ($p < 0.05$). Effect size of 0.40 for pain reduction, 0.32 and 0.38 for improving physical function and stiffness, respectively. | 4.76% patients in experimental group experienced adverse reactions as compared to 0% in placebo group. |
| [66] | 60; 54 | Knee OA | 1:1 | Aflapin®; 100mg/day; 30 days | Placebo | Functional disability | ***Significant improvements in pain and function scores*** were observed in treatment group supplemented with 100 mg/day of Aflapin when compared to either baseline or placebo. | No SAEs reported |
| [80] | 92; 60 | Knee OA | 1:1 | HLXL capsules; 4000 mg/day for week 1 and 2, and 5600 mg/day for week 3 to 8; 8 weeks | Placebo | Changes in the VAS version of WOMAC pain and function score | ***No significant between-group differences*** in all outcomes evaluated. | HLXL: 35 AEs reported Placebo: 29 AEs reported |

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| [67] | 133; 65 | Knee OA | 1:1 | 4Jointz cream; 3.5 g/day; 12 weeks | Placebo | 4Jointzwas superior to placebo at 12 weeks for change in: knee pain using the pain intensity VAS and the pain scale from the KOOS Questionnaire; markers of inflammation (IL-6), and cartilage breakdown (CTX-2). | ***Pain scores significantly reduced*** in the group who received 4Jointz compared to the group who received placebo after 12 weeks using both the VAS (-9.9 mm, p=0.034) and the KOOS pain scale (+5.7, p=0.047). Changes in IL-6 and CTX-2 were not significant (-0.04, p=0.5; -0.01, p=0.68). | Local rash that was more common amongst participants receiving 4Jointz (21% vs 1.6%, IRR 13.2, p= 0.013) |
| [84] | 198; 62 | Knee OA | 1:1 Doubledummy. Non-inferiority. | GCSB-5; 600mg/day; 12 weeks | Celecoxib | Change in total WOMAC score | GCSB-5 is **comparable** to Celecoxib in terms of the efficacy and safety. | Incidence of ADRs were 31.3% and 21.2% in experimental and control group respectively |
| [74] | 59; 63 | Knee OA | 1:1 | Topical Gln and chondroitin preparation; 8 weeks | Placebo | Participant pain rating based on a 100 mm VAS that was assessed in the clinic at 0, 4, and 8 weeks | VAS scores indicated a ***greater mean reduction in pain*** for experimental group compared to placebo after 8 weeks. After 4 weeks the difference between active and placebo groups in their mean reduction from baseline was 1.2 ($p < 0.05$) and after 8 weeks was 1.8 ($p < 0.01$). | AEs appeared to be of a minor nature and were equally distributed between the 2 groups |
| [81] | 1583; 59 | Knee OA | 1:1:1:1 | Gln; 500mg/day; 24 weeks + CSPG/ 400 mg/day; 24 weeks | 1. Placebo 2. Gln 3. CSPG 4. Celecoxib | 20% decrease in the summed score for WOMAC pain subscale from baseline to week 24 | ***No significant difference*** between treatment and placebo in reducing knee pain by 20%. | AEs were mild, infrequent, and evenly distributed among the groups. |
| [82] | 95; 54 | Knee OA | 1:1 | Reparagen; 1800mg/day; 8 weeks | Gln; 1500 mg/day; 8 weeks | Response rate based on a 20% | The response rates were ***substantial*** for both glucosamine and reparagen. | No SAEs were noted |

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| | | | | | | improvement in WOMAC pain scores | | |
| [72] | 50; 68 | Knee OA | 1:1 | MSM; 1.125 grams 3 times daily; 12 weeks | Placebo | WOMAC, ALF, SF-36, and VAS | ***Significant difference*** between treatment groups over time in WOMAC physical function (p = 0.04) and in WOMAC total score (p = 0.03). No significant differences between groups in WOMAC pain (p = 0.08), WOMAC stiffness (p = 0.08), SF-36 total score (p = 0.54). | No AEs recorded |
| [85] | 64; 69 | Knee OA | 1:1 Non-inferiority. | Collagen MD-Knee; two vials for a total of 4 ml via intra-articular injection, once a week; 5 weeks | Intra-articular injection of sodium hyaluronate | LKI at T0, 3 month and 6 month follow-up | Treatment with MD-Knee was ***not inferior*** of the treatment with SUPARTZ® (sodium hyaluronate). | 1 subject discontinued for a moderate post-injection reaction in experimental group |
| [73] | 69; 52 | Knee OA | 1:1 | L-carnitine Tartrate; 750 mg /day divided into 3 equal doses of one 250-mg tablet; 8 weeks | Placebo | Pain intensity assessed using a 0- to 100-mm VAS scale and PGA of the severity of knee OA | ***Significant difference*** between the 2 groups for mean pain intensity and PGA of the severity of knee OA ($p < 0.05$) | No participants reported any AEs |
| [69] | 215; 60 | Hand OA | 1:1 | Oral GCSB-5; 600 mg/ day; 12 weeks | Placebo | Change in AUSCAN pain score at 4 weeks relative to baseline | ***Improvements*** in the AUSCAN pain score were ***significantly greater*** in the GCSB-5 group than in the placebo group over the 16-week study period (P = 0.0052). . | AE GCSB-5: 55% Placebo: 45% |
| [16] | 345; 62 | Hip OA | 1:1 | Avocado–soybean unsaponifiable—Expanscience (ASU-E); | Placebo | Mean change in JSW on the AP target hip view at year 3 | ***No statistically difference*** in adjusted mean JSN at year 3 (p=0.72). | 10.1% patients in experimental group has ≥1 treatment related AEs |

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| | | | | 300mg/day; 3 years | | | | | compared to 6.2% in control |
| [70] | 94; *age not reported* | Knee and hip OA | 1:1 | Rose-hip; 5g/day; 3 months | Placebo | Pain, stiffness, disability, and global severity of disease assessed using WOMAC | WOMAC pain, disability, stiffness, and global severity of the disease ***decreased significantly*** (p< 0.014, p<0.018, p<0.038, and p<0.035, respectively) after 3 months. | No SAEs in experimental group |
| [71] | 78; 53 | Knee and hip OA | 1:1 | Willow bark extract; 240 mg salicin/day; 2 weeks | Placebo | Pain dimension of the WOMAC OA Index | ***Significant difference*** between the active treatment and the placebo group was observed in the WOMAC pain dimension (d =6.5 mm, 95% CI= 0.2–12.7 mm, p = 0.047) | Skin rash starting in a patient in experimental group |
| **Megavitamin therapy** | | | | | | | | | |
| [94] | 34; 51.7 | FM | 1:1 | IV Myers' cocktail; Once weekly; 8 weeks | Placebo | TPI | Between-group comparisons of all primary outcomes did ***not reach statistical significance*** (all *p* > 0.05). | 1 AE in experimental group |
| [92] | 40; 19 | Juvenile SLE | 1:1 | Oral cholecalciferol; 50,000 IU/week; 24 weeks | Placebo | SLEDAI and ECLAM | At the end of the intervention, a ***significant improvement*** in SLEDAI (p=0.010) and in ECLAM (p=0.006) was observed in the experimental group compared to the placebo group. | No SAEs reported |
| [95] | 167; 12 | Juvenile RA | 1:1 | Ca; 1,000 mg/day and vitamin D; 400 IU/day; 24 months | Placebo | Total body BMD | ***Significantly higher total body BMD*** among patients who received Ca compared with patients who received placebo during the study period (p= 0.03) | No SAEs reported |
| [93] | 58; 39 | RA | 1:1 | Vitamin $K_1$; 10mg/day; 8 weeks | Placebo | Serum levels of MMP-3, and RF | ***No significant differences*** in serum MMP-2 and RF between groups | 1 participant in experimental group |

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| | | | | | | | | experienced heartburn |
| [88] | 599; 63 | Knee OA | 1:1 | Vitamin D3; 50,000 IU/ month; 24 months | Placebo | WOMAC knee pain score and change in tibial cartilage volume on MRI | ***No significant difference*** in change in MRI-measured tibial cartilage volume or WOMAC knee pain score over 2 years | 4 participants developed hypercalcemia in the vitamin D group vs 2 in the placebo group |
| [89] | 103; 53 | Knee OA | 1:1 | Oral cholecalciferol; 60,000 IU/day for 10 days followed by 60,000 IU once a month for 12 months | Placebo | Knee pain and function | At 12 months, ***knee pain had decreased*** in the vitamin D group by mean -0.26 on VAS and -0.55on the WOMAC, whereas in the placebo group, it increased by mean 0.13 on the VAS and 1.16 on the WOMAC (effect size = 0.37 and 0.78). ***Knee function improved*** in the vitamin D group by mean -1.36 over the placebo group which had a mean 0.69 (effect size = 0.06). | Not reported |
| [90] | 136; 64 | Knee OA | 1:1 | Vitamin E; 500 IU/day; 24 months | Placebo | Change in knee cartilage volume | ***No significant difference*** was found between the two groups for change in knee cartilage volume. | AEs not reported |
| [91] | 22; 63 | Knee OA | 1:1 | Aquamin; 2400 mg/d; 12 weeks | Placebo | WOMAC | ***No significant difference*** was found between the two groups for WOMAC pain, stiffness, activity or composite scores. | AEs profiles were not significantly different between the groups |
| **Chiropractic or osteopathic manipulation** | | | | | | | | |
| 43; 45 | Knee OA | 1:1 | Kinesio taping using “Y-strip”; every | Sham taping using flexible tape | Pain intensity with activity and at night using VAS | ***No significant difference*** between the groups VAS for activity pain, VAS for nocturnal pain. | Not reported | |

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| | | | four days, three time | | | | | |
| 60; 82 | CMC joint OA | 1:1 | Multimodal manual treatment; 12 sessions; 4 weeks | Sham treatment with ultrasound at 0 watts/cm$^2$ | Pain intensity of the first CMC joint assessed using VAS | Patients in the experimental group experienced a ***significantly greater reduction in pain*** compared to the placebo group ($p<0.001$). | No AEs detected | |
| 28;82 | TCOA | 1:1 | Maitland's passive accessory mobilization; 4 sessions; 2 weeks | Sham treatment with ultrasound at 0 watts/cm$^2$ | Pain threshold measurement | In the treated group, ***pain threshold in the TMJ increased*** after treatment and was maintained at the same level during the first FU and second FU. All values in sham group remained unchanged. | No AEs detected | |
| **Energy healing therapy** | | | | | | | | |
| [99] | 45; 68 | OA | 1:1 Crossover | Magnetic wrist strap; minimum of 8 hours/day; 4 weeks | Weak magnetic wrist strap | WOMAC OA Index, McGill Pain Questionnaire — PRI, a pain VAS, and medication use | ***No significant difference*** was observed between devices in terms of their effects on pain as measured by the primary outcome measure (WOMAC A), the PRI and the VAS as well as stiffness, physical function, and medication use. | No AEs reported |

Abbreviations

ACPA: Anti-citrullinated protein antibodies; ACR20: American College of Rheumatology 20% improvement criteria; ADR: Adverse drug reaction; AE: Adverse event; AIMS2: Arthritis Impact Measurement Scale; ALA: Alpha-lipoic acid; ALF: Aggregated Locomotor Function; AP: Anteroposterior; AUSCAN: Australian Canadian Osteoarthritis Hand Index; BDI: Back Depression Inventory; BMD: Bone mineral density; BPI: Brief Pain Inventory; Ca: Calcium; CES: Cranial electrical stimulation; CD: Cluster of differentiation; CDAI: Clinical Disease Activity Index; CI: Confidence interval; CMC: Carpometacarpal; CPAQ: Chronic Pain Acceptance Questionnaire; CRP: C- reactive protein; CSPG: Chondroitin sulfate; DAS: Disease activity score; DER: Drug-to-extract ratio; DHA: Docosahexaenoic acid; DHEA: Dehydroepiandrosterone; DI: Disability index; dPP: Dietary plant- derived polysaccharides; EA: Electroacupuncture; ECLAM: European Consensus Lupus Activity Measurement; EF-HVAC: Electric field by high voltage alternating current; EPA: Eicosapentaenoic acid; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism response criteria; FAS: Full analysis set; FIQ: Fibromyalgia Impact Questionnaire; FM: Fibromyalgia; fMRI: functional magnetic resonance imaging; FRAP: Ferric-reducing/antioxidant power; FU: Follow-up; GA: Global assessment; GHQ: General Health Questionnaire; GLA: Gamma-linolenic acid; Gln: Glucosamine; GTT: *Glucosidorum Tripterygll* Totorum; HAI: Hand algofunctional index; HAQ: Health assessment questionnaire; Hb: Hemoglobin; hs-CRP: high-sensitivity C-reactive protein; HSQ: Health status questionnaire; HLXL: Huo-Luo-Xiao-Ling; IBS-C: constipation-predominant Irritable bowel syndrome; IL: Interleukin; IRR: Incident rate ratio; ITT: Intention-to-treat; IU: International unit; IV: Intravenous; JSN: Joint space narrowing; KOOS: Knee Injury and Osteoarthritis Outcome Score; LFI: Lequesne's Algofunctional Index; LKI: Lequesne Knee Index; LWDHW: Liu-Wei-Di-Huang Wan; MMP-3: Matrix metalloproteinase-3; MPQ: McGill Pain Questionnaire; MPS: Myofascial pain syndrome; MSM: Methylsulfonylmethane; MTS: Medial tenderness score; MTX: Methotrexate; NHP: Nottingham Health Profile; NK: Natural killer; NRS: Numeric Rating Scale; NSAID: Non-steroidal anti-inflammatory drug; NO: Nitric oxide; OA: Osteoarthritis; OMERACT-OARSI: Outcome Measures in Rheumatology–OA Research Society International; PANAS: Positive and Negative Affect Scales; PCS: Pain Catastrophizing Scale; PGA: Patient global assessment; PGWBI: Psychological General Well Being Index; POMS: Profile of Mood States; PPS: Per-protocol set; PRI: Pain Rating Index; pVAS: Pain on movement; QoL: Quality of Life; RA: Rheumatoid arthritis; RF: Rheumatoid factor; RR: Risk ratio; SAE: Serious adverse event; SF36: Short form health survey; SGPT: Serum glutamic pyruvic transaminase; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SMS: San Miao San; SPPB: Short Physical Performance Battery; SRL: Spiroflor; SSZ: Sulfasalazine; SOD: Superoxide dismutase; TAC: Total antioxidant capacity; TCA: Traditional acupuncture; TCOA: Thumb carpometacarpal osteoarthritis; TLHS: Tong Luo Hua Shi; TMJ: Trapeziometacarpal joint; TNF: Tumour necrosis factor; TPI: Tender point index; VAPS: Visual analog pain scale; VAS*: Visual analog scale*; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; YSJB: Yi Shen Juan Bi