



SYSTEMATIC REVIEW AND META-ANALYSIS

What do we know about some popular methods of complementary and alternative medicine: An overview of Cochrane systematic reviews

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Abstract

Objective: This study aims to investigate the level of evidence on the effectiveness and safety of 14 complementary and alternative medicine (CAM) methods that were legalized in Türkiye (Turkey).

Methods: A systematic literature search was conducted in the Cochrane Systematic Review Database for acupuncture, apitherapy, hypnotherapy, leech therapy, homeopathy, cupping therapy, chiropractic, prolotherapy, osteopathy, maggot therapy, mesotherapy, music therapy, reflexology, ozone therapy. After screening, 178 studies were included in the qualitative synthesis. Evidence quality was classified as 'high/moderate/low'. AMSTAR-2 was used to evaluate the quality of systematic reviews. This study was registered to PROSPERO(CRD42019127509).

Results: There are 16 low (LQE) and four moderate-quality evidence (MQE) of effectivity for various conditions were found for acupuncture, while it has no effectivity on 13 conditions. There are six LQE and one MQE on its safety. One study found high-quality evidence of the effectivity of apitherapy concluded honey accelerates healing of burn wounds. Thirteen LQE and three MQE showed the effectiveness of music therapy, while one study reported it as ineffective. Four studies found LQE showing hypnotherapy might be effective in some conditions, and one study found it was ineffective. Regarding osteopathy, one study found MQE, and one study found LQE. One study reported LQE for the effectiveness of chiropractic. The only evidence for the effectivity of homeopathy is of low quality and four studies have shown that it is not effective.

Conclusions: Since there is insufficient evidence, 14 CAM methods legalised in Türkiye should not be used in routine medical practice. Future researches aiming to produce high-quality evidence are needed.

Keywords: Complementary Medicine, Alternative Medicine, Effectivity, Safety, Systematic Review

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INTRODUCTION

Definitions

Today an important consideration in healthcare is the increasing popularity of various approaches to disease treatment referred to as 'complementary', 'alternative', 'traditional', or 'holistic' medicine, to distinguish them from 'conventional' or 'modern' medicine based on scientific knowledge. The definitions of those approaches, the applications they cover, and their indications may differ according to geography, local culture, and national regulations; there are no universal standards governing their use. When a non-mainstream practice is used together with conventional medicine, it is categorized as "complementary". When a non-mainstream practice is used instead of conventional medicine, it is considered to be "alternative".¹ According to another definition, treatments applied by complementary medicine have little in common other than their exclusion from the mainstream. They tend to be embedded in primary care systems of medicine (including traditional Chinese medicine and Ayurvedic medicine, which have unique diagnostic criteria, diverse therapeutic options, and discrete therapies - including shark cartilage, bee pollen, ozone therapy, and almost everything in between).² Moreover, the scope of definitions can also vary depending on the context. For example, acupuncture can be used as a complementary treatment for infertility, while it is often used as an alternative to physiotherapy in cases of low back pain.³ In this study, the term "complementary and alternative medicine" (CAM) was chosen mainly because it covers all practices aforementioned, including the traditional ones.

Usage

According to the WHO, "Given the unique health challenges of the 21st century, interest in CAM is undergoing a revival".⁴ In addition, because such practices are being used for purposes such as reducing healthcare costs or creating a new way of dealing with chronic diseases, CAM is becoming legal in many countries.^{5,6} According to the American National Health Statistics reports, 34% of those over the age of 18 have used some method of complementary medicine. The most commonly used modalities are vitamin and non-mineral nutritional supplements, breathing exercises, yoga, Tai Chi, Qi Gong, chiropractic, and osteopathic practices.⁷ It has been reported that 1 out of every 5 people aged four and over is using complementary methods, and out-of-pocket spending is about USD 30 billion annually. This constitutes 1% of total health expenditures, 9% of mobile health expenditures, and 30% of conventional doctor visits expenditures.⁸ The prevalence of CAM use in the European Union was reported as 0.3-86%, with the most frequently used CAM applications being herbal medicine, homeopathy, chiropractic, acupuncture, and reflexology.⁹ In a national study in Australia, the percentage of people using any vitamin support, massage therapy, meditation, herbal medicine, aromatherapy, chiropractic, yoga, naturopathy, acupuncture, energy healing, homeopathy, qi gong, martial arts, tai chi, osteopathy, reflexology, and Chinese medicine diet therapy was found to be 68.9%.¹⁰ In the same research, the proportion of adherents to any kind of CAM practitioner was 44.1%, which corresponds to about 69.2 million people. According to a national study in Canada, 12.4% of people over the age of 12 visited a CAM practitioner at least once

a year.¹¹ The most commonly used CAM methods are massage therapy, acupuncture, homeopathy, chiropractic, herbal medicine, reflexology, and spiritual healing, respectively.

CAM usage in Turkiye (formerly Turkey) should also not be underestimated. According to a study conducted nationwide, CAM usage in Turkiye is 60.5%.¹² These modalities are more frequently used by women and people over the age of 35; however, levels of education and income did not affect CAM usage. Research carried out at the local level found that CAM is used by 22-61% of oncology patients¹³⁻²³, 13-52% of dermatology patients²⁴⁻²⁶, 58% in lumbar disc hernia cases²⁷, 47% of rheumatoid arthritis patients²⁸, 22% of psychiatric patients²⁹, 72% of chronic obstructive pulmonary disease cases³⁰, 63% of asthma patients³⁰, 25% of chronic kidney failure cases³¹, 35-41% of diabetes mellitus patients^{32, 33}, 31% of patients with allergic diseases³⁴, and 82% of infertility cases.³⁵

Regulations

Regulations regarding CAM methods -which cover a wide range of modalities including plants, yoga, leeches, body manipulations, and even 'astral travel' - are not standardized in most countries of the world. For instance, permitted CAM practices, and the professions of people who may use those methods, differ significantly by the state in the United States.³⁶ In the European Union, 18 of 29 countries have specific regulations, and these differ among countries due to the diversity of cultures and traditions.³⁷

In Turkiye, 15 CAM methods (Acupuncture, Apitherapy, Phytotherapy, Hypnosis, Leech application, Homeopathy, Chiropractic, Cup practice, Maggot therapy, Mesotherapy,

Prolotherapy, Osteopathy, Ozone application, Reflexology, and Music Therapy) were legalized in 2014 by the Regulation on Traditional and Complementary Medicine Practices and permitted to be used for over 200 indications.³⁸ Some of those indications are medical diagnoses while others are symptoms or merely complaints such as "acute and chronic neck and low back pain" or "Recurrent head, neck, back and lower back pains" (Listed in Annex 3 of the Regulation).

Aim of the study

To be able to apply a medical modality to the human body, sufficient scientific evidence is required to ensure that the expected benefit from that method will be higher than the possible risks. The use of CAM methods is increasing worldwide, however, the scientific validity of those applications is still a subject of considerable debate as there has not been an adequate investigation into the sufficiency of evidence for the safety and effectiveness of CAM modalities.² Our knowledge of the extent to which these practices are beneficial or pose risks is limited. Another factor that complicates the problem is that scientific skepticism might be left aside and such practices are declared quackery completely. Therefore, answering the question "what do we know about the safety and effectiveness of CAM methods?" has vital importance for public health. This study is structured in the context of that question. This study is structured in the context of that question, and aims to explore whether there is sufficient evidence on the popular CAM methods.

METHODS

This review includes 14 CAM methods (Acupuncture, Apitherapy, Hypnotherapy, Leech therapy, Homeopathy, Cupping therapy,

Chiropractic, Prolotherapy, Osteopathy, Maggot therapy, Mesotherapy, Music therapy, Reflexology, and Ozone therapy) which were legally permitted in Türkiye since 2014 and are also increasingly popular in the world. Phytotherapy methods were excluded from the study since the evidence base of the herbal medicine is more solid and frequently compellingly positive.²

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the process.³⁹ The review protocol was registered at the International Prospective Register of Systematic Reviews PROSPERO (CRD42019127509).

Search Strategy

We conducted literature searches in the Cochrane Database of Systematic Reviews to identify all the systematic reviews (SRs) about the included CAM methods for any health condition. Searches for SRs and meta-analyses were conducted between 20 December 2021 - 28 February 2022. The keywords were “acupuncture OR acupuncture therapy OR acupuncture points OR needle OR electro-acupuncture OR auricular acupuncture OR warm-acupuncture OR dry needling OR trigger-point therapy OR moxibustion”, “apitherapy OR bee venom OR honey OR apipuncture”, “hypnotherapy OR hypnosis OR trance”, “leeches OR leeching OR leech therapy OR hirudo medicinalis OR leech”, “homeopathy OR homeopathic OR homeopathic OR homeopathy OR homeopathic medicines OR homeopath”, “chiropractic OR spinal manipulation”, “dry cupping OR wet cupping OR cupping therapy”, “prolotherapy OR regenerative injection therapy OR intraarticular injections”,

“osteopathy OR osteopathic manipulative treatment OR OMT OR osteopathic medicine OR osteopath”, “maggot therapy OR maggot debridement therapy OR larval therapy OR larval debridement therapy”, “mesotherapy OR intradermal therapy OR intradermotherapy”, “musico-therapy OR musico-therapies OR music OR music therapy OR music therapies”, “reflexology OR reflex therapy OR reflexotherapy”, “ozone-therapy OR ozonotherapy OR ozone OR ozone therapy”.

Inclusion and Exclusion Criteria

The SRs evaluating the effectiveness and/or safety of the selected CAM methods were included in the study. Interventions were compared to placebo, no treatment, or another intervention/drug. There were no date restrictions, but we have included the SRs in English only. The SRs (with or without meta-analysis) that involved any type of human and/or animal trials were included. Cochrane protocols, trials, editorials, special collections, clinical answers, non-systematic reviews, and withdrawn reviews were excluded.

Study Selection

Abstracts and full texts were reviewed by two authors. We were able to collect 811 studies in the beginning. After exclusions, 178 studies were enrolled for review, as shown in the PRISMA flowchart (Fig.1).

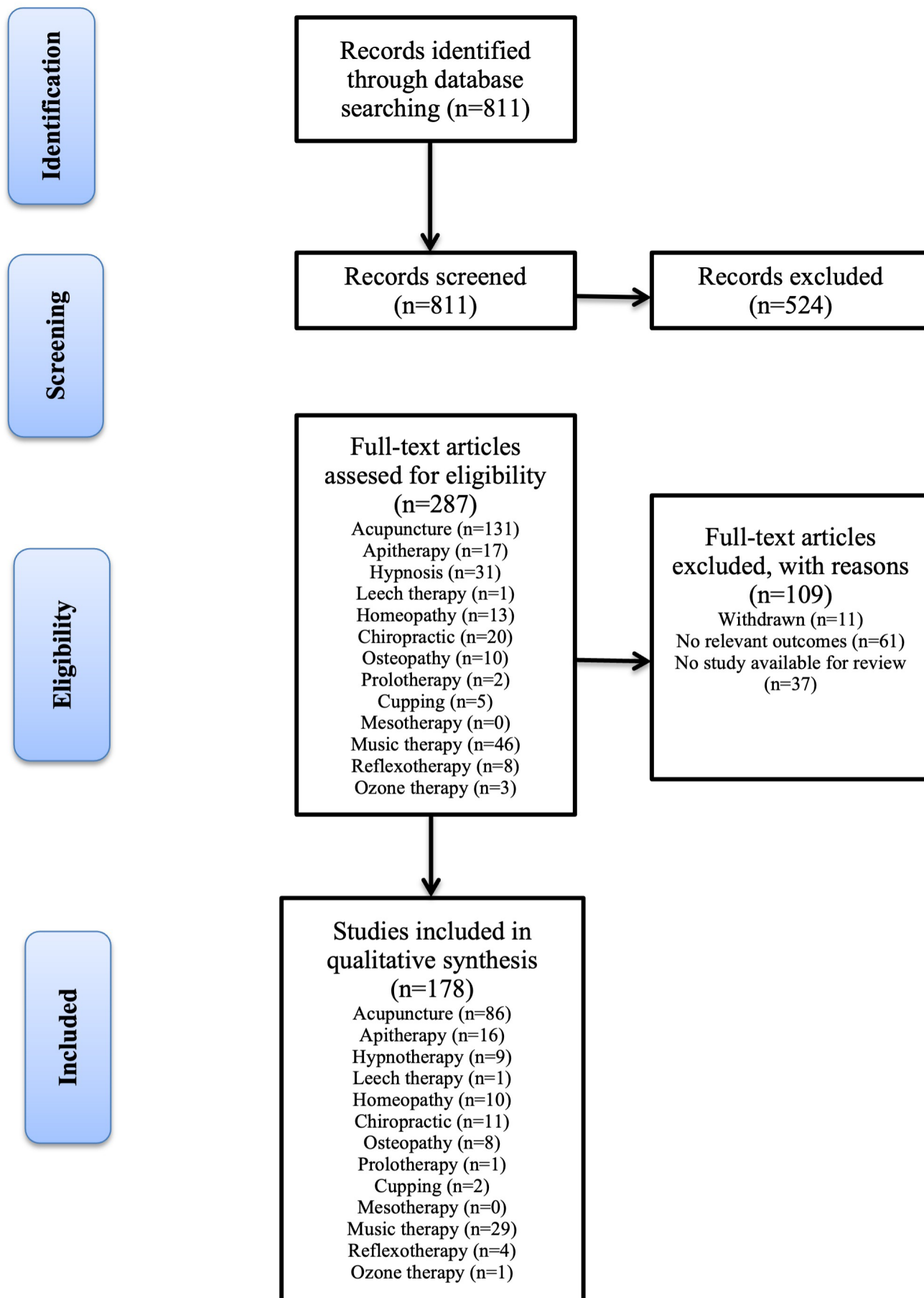


Fig.1 PRISMA flow diagram of the study

Data extraction

Included characteristics of the studies during the process were the year of publication, the total number of the participants, the total number of the included trials, health condition, type of intervention, controls, reported quality of the evidence (QoE), main outcomes of the safety and effectiveness. Extractions were made by one author (PET) and were verified for accuracy by the other author (MMC).

Quality Assessment of the Evidence Levels

In this review, findings were represented with evidence levels that were reported in each study enrolled. QoEs were evaluated by the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach. The GRADE system has four quality levels:⁴⁰

- High: Randomized trials; or double-upgraded observational studies.
- Moderate: Downgraded randomized trials; or upgraded observational studies.
- Low: Double-downgraded randomized trials; or observational studies.
- Very low: Triple-downgraded randomized trials; or downgraded observational

studies; or case series/case reports.

With the GRADE approach, researchers can lower the level of randomized controlled trials or increase the level of observational studies due to some characteristics of studies (Table 1).⁴⁰

QoE and strength of recommendations were set by the GRADE Working Group as below:⁴¹

- High = Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low = Any estimate of effect is very uncertain.

We classified the very low and low QoEs as 'low quality'; in total, we had three QoE groups. To determine whether a CAM method can be applied effectively and safely, we took into consideration the recommendations above, and the level of "High-quality" was accepted

Table 1. Factors that can increase/decrease the quality level of a body of evidence

Increasing factors	Decreasing factors
<i>Large magnitude of effect</i>	<i>Limitations in the design and implementation of available studies suggesting high likelihood of bias</i>
<i>All plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect</i>	<i>Indirectness of evidence (indirect population, intervention, control, outcomes)</i>
<i>Dose-response gradient</i>	<i>Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses)</i>
	<i>Imprecision of results (wide confidence intervals)</i>
	<i>High probability of publication bias</i>

as the requirement for clinical usage.

Quality Assessment of The Included SRs

We assessed the quality of the SRs with the Assessment of the Methodological Quality of Systematic Reviews (AMSTAR-2) tool. AMSTAR was developed to evaluate SRs of randomized trials. AMSTAR-2, as the revised form of AMSTAR, retains 10 of the original domains. AMSTAR-2 is a 16-item tool that rates overall confidence in the results of the review as high, moderate, low, critically low, and not intended to generate an overall score.⁴²

Data Analysis

This study is a qualitative systematic review that includes summarizing the outcomes of the individual SRs and presenting them using separate tables for each therapy method. Performing a quantitative analysis was not applicable.

RESULTS

Acupuncture

Among 86 studies concerning acupuncture modalities, 4 reported moderate-quality evidence (MQE) and 19 reported low-quality evidence (LQE) for acupuncture practices' possible effectivity (Supplement Table at the end of the article). There were MQE for the effectivity of acupuncture in episodic migraine prevention⁴³, tension-type headache prevention⁴⁴, changing the presentation of an unborn baby in the breech position⁴⁵, and decreasing prostatitis symptoms⁴⁶. LQEs involved premenstrual syndrome symptoms⁴⁷, pain management during labour⁴⁸, preventing nausea and vomiting in women undergoing regional anaesthesia for cesarean section⁴⁹, fatigue, depression, sleep disturbance, uremic pruritus in haemodialysis patients⁵⁰, chronic

nonspecific low back pain⁵¹, acute hordeolum⁵², acute traumatic brain injury management⁵³, acute stroke⁵⁴, depression⁵⁵, schizophrenia⁵⁵, stroke rehabilitation⁵⁶, fibromyalgia⁵⁷, nocturnal enuresis⁵⁸, endometriosis⁵⁹, taste disturbances⁶⁰, recurrent urinary tract infection prevention⁶¹, chemotherapy or radiotherapy side effects in cancer patients⁶², fatigue in inflammatory bowel disease⁶³, anaesthesia induction in children⁶⁴, and postoperative nausea and vomiting prevention⁶⁵. Twelve studies have shown there could be a possible effect from acupuncture treatment, but these studies were not clear about evidence quality. The remaining studies were not able to draw an exact conclusion.

It has been shown that acupuncture has no effect on assisted reproduction⁶⁶, autism spectrum disorders⁶⁷, epilepsy⁶⁸, hypertension⁶⁹, stress urinary incontinence⁷⁰, cocaine dependence⁷¹, dry mouth⁷², hyperemesis gravidarum⁷³, hot flashes in women with a history of breast cancer⁷⁴, chronic pain in people with spinal cord injury⁷⁵, carpal tunnel syndrome⁷⁶, labour induction⁷⁷, and cancer pain⁷⁸.

There were no studies that showed acupuncture as unsafe. But evidence about safety was limited; six studies had LQE, and only one study had MQE on safety. The MQE study examined the use of acupuncture for episodic migraine prevention⁴³. Studies that reported LQE regarding safety involved the use of acupuncture for premenstrual syndrome symptoms⁴⁶, acute stroke⁵³, hip osteoarthritis⁷⁹, schizophrenia⁵⁵, stroke rehabilitation⁵⁶, and fibromyalgia⁵⁷.

Apitherapy

In total 16 studies about apitherapy were included in this study. One study had high-

quality evidence (HQE), two had MQE, and three had LQE about the effectiveness of apitherapy practices. HQE was presented in connection to 'honey healing burns more quickly than non-antibacterial treatments'.⁸⁰ There were MQEs for honey's effectiveness in relieving cough symptoms⁸¹ and healing surgical wounds with honey-soaked gauze⁸². Low-quality evidence involved honey healing burns more quickly than silver sulfadiazine⁸³, bee venom reducing acne scars⁸⁴, and honey preventing oral mucositis for patients receiving cancer treatment.⁸⁵ Five studies showed there was no significant effect of apitherapy treatments and the remaining studies were not able to create clear conclusions. There was no evidence to support the effectiveness of honey for short-term wound healing⁸³, preventing infectious complications in haemodialysis patients with central venous catheters⁸⁶, healing venous leg ulcers⁸⁷, reducing infection rates, pain, or healing time of ingrowing toenails⁸⁸, and reducing exudate, malodor, and wound pain of fungating wounds.⁸⁹

Some studies reported results about safety, but the evidence level was not clear. In one study, it was reported that systemic adverse reactions occurred in approximately 3 out of 20 patients treated with bee venom.⁹⁰

Music Therapy

Among 29 studies, three reported MQE, and 14 reported LQE on the effectiveness of music therapies. Six studies showed there might be effects from music interventions but didn't classify the quality of evidence, and five studies were not clear about the conclusions. One study did not find any significant effect of music therapy on the condition of 'Auditory integration training for autism spectrum

disorders'.⁹¹ Studies with MQE involved insomnia⁹², improving social interaction and communication in children with autism spectrum disorder⁹³, schizophrenia and schizophrenia-like disorders.⁹⁴ Studies with LQE evaluated reducing anxiety in women undergoing colposcopy⁹⁵, improving maternal and infant outcomes during caesarean section⁹⁶, stress and anxiety reduction in coronary heart disease patients⁹⁷, acquired brain injury⁹⁸, improving psychological and physical outcomes in cancer patients⁹⁹, anxiety management in mechanically ventilated patients¹⁰⁰, preoperative anxiety¹⁰¹, depression¹⁰², dementia¹⁰³, alleviating pain during orthodontic treatment¹⁰⁴, sleep promotion in the intensive care unit¹⁰⁵, post-caesarean pain¹⁰⁶, pain management in labour¹⁰⁷, and chronic obstructive pulmonary disease¹⁰⁸.

There was no study that reported music interventions as unsafe. Some studies mentioned safety but didn't have any information regarding evidence quality. One study reported LQE about the safety of music therapies.¹⁰⁸

Hypnotherapy

There were nine included studies about hypnotherapy. Four of them reported LQE and another four studies reported evidence without suggesting quality. One study revealed that there was no significant effect and other studies were uncertain about the effectivity. LQE results included nocturnal enuresis in children⁵⁸, antipsychotic-induced tardive dyskinesia¹⁰⁹, needle-related procedural pain and distress in children¹¹⁰, reducing pain in the short term in children and adolescents presenting with recurrent abdominal pain¹¹¹. There was no effect from hypnotherapy in

reducing chronic pain in people with spinal cord injury.⁷⁵

Some studies mentioned the safety of hypnotherapy, but no study presented evidence on this subject.

Osteopathy

Among the eight studies, one reported MQE, and another reported LQE about the effectiveness of osteopathic practices. The MQE study was about low-back and pelvic pain during pregnancy¹¹² and the LQE study was about pneumonia in adults¹¹³. Five studies showed there was no evidence to suggest osteopathy is effective for dysmenorrhea¹¹⁴, asthma¹¹⁵, abdominal pain in Crohn's disease and inflammatory bowel disease¹¹⁶, chronic low-back pain¹¹⁷, and acute low-back pain¹¹⁸. The other study didn't yield any clear results.

Chiropractic

Among the 11 studies included, one study reported LQE about the effectiveness of chiropractic practices. Four studies revealed there was no significant effect and one study reported possible effectiveness without evidence quality information. The LQE study was about nocturnal enuresis in children.⁵⁸ No significant effect was demonstrated for asthma¹¹⁵, chronic low-back pain¹¹⁷, acute low-back pain¹¹⁸, and dysmenorrhea¹¹⁴. Some studies mentioned the safety of chiropractic practices, but there was no information on evidence quality.

Homeopathy

Among 10 studies, one study was able to show the effectiveness of homeopathy with LQE. Another study reported possible effectivity with no information on the quality of evidence. Four studies showed there was no significant effect from homeopathic

treatments, and the others were not able to draw any clear conclusions. The LQE study involved homeopathic *Calcarea carbonica* for cutaneous molluscum contagiosum treatment.¹¹⁹ The studies that reported homeopathic practices as 'having no effects' were about preventing and treating acute respiratory tract infections in children¹²⁰, chronic asthma¹²¹, labour induction¹²², and hot flashes in women with a history of breast cancer.¹²³ There was only one certain piece of evidence about the safety of homeopathy, and it was a study with low-quality of evidence.¹²⁰

Prolotherapy

One study was available for prolotherapy practices. The study was about chronic low-back pain, and it did not draw an exact conclusion about its effectiveness and safety.¹²⁴

Cupping

There were two studies included in this review study, and both were unable to show any significant effect of cupping practices. Study subjects included acne vulgaris¹²⁵, and reducing respiratory morbidity in infants requiring ventilatory support¹²⁶ Also, these studies did not present any clear evidence about safety, while one of them reported there were mild adverse reactions to wet cupping.⁸⁴

Leech Therapy

We were able to collect one study only, and it was about lateral elbow pain treatment.¹²⁷ That review included one study that reported a significant difference between groups (leech vs. NSAID) favouring leeches in total pain score. Also, there were significantly fewer skin reactions in the topical NSAID group. The quality of the evidence is unknown.

Maggot Therapy

There was only one study included in the review, and it was about debridement of diabetic foot ulcers. It found that one small trial suggested that larvae were better in wound area reduction compared to hydrogel.¹²⁸ There was no data about safety.

Reflexology

Four studies about this subject were suitable for the review. One study showed that reflexology has no benefit for fatigue in rheumatoid arthritis.¹²⁹ Other studies did not have any exact conclusions. No exact evidence about the safety of reflexology was represented.

Mesotherapy

There was no study available on this subject in the Cochrane Database of Systematic Reviews.

Ozone Therapy

There was one study reporting that ozone therapy could be effective in the treatment of foot ulcers in people with diabetes, but the quality of evidence is unknown.¹³⁰

DISCUSSION

Every medical intervention carries a risk of harm. Given these risks, to be able to take any action on the human body, the expected benefit must be greater than the possible harm. This crucial understanding is emphasized by the ethical principles of *Non-maleficence* (First do no harm!) and *Beneficence* (Duty to be useful). This evaluation can be made most reliably by using scientific knowledge. Additionally, the quality of evidence, which is dependent on the type of method used to produce scientific knowledge, is also important. Within the current evidence-based medicine approach, an intervention should not be performed if it

has been shown that it is not effective or safe because the probability of harm is greater in such cases. An intervention should also not be performed if sufficient evidence on its safety and effectiveness does not exist because the expected benefit / possible harm assessment cannot be made. It means that we may be putting the patient and/or public health at great risk, an unacceptable practice due to the primary ethical principles of scientific medicine and the right to health.

Based on the understanding summarized above, this study aimed to investigate current evidence on the effectiveness and safety of 14 legalized CAM methods in Turkiye for indications listed in the related Regulation. To that end, we carried out a systematic review in the Cochrane Database of Systematic Reviews and found that there is no study with HQE or MQE in the Database on both the effectiveness and safety of the CAM methods investigated. In sum, the current evidence in the Cochrane Database on safety and effectiveness is not enough to justify the application of those 14 CAM modalities for treating any disease or symptom.

However, these modalities have been legalized in Turkiye with the "Regulation on Traditional and Complementary Medicine Practices" issued by the Ministry of Health in 2014. One of the criteria considered when deciding which methods to legalize was how many publications on that method were available in PubMed and the Cochrane Library.¹³¹ However, considering the number of the publications alone is not scientifically appropriate, and, as our study shows, the evidence in Cochrane is not sufficient to support the use of these methods. Similarly, in concordance with the findings of this study, an analysis of the

comprehensive book on 685 CAM methods/condition pairings found that only 7.4% of them were based on sound evidence.¹³² It was emphasized that even that percentage might be a gross over-estimation for a range of reasons; for example, several of the included modalities, such as exercise, massage, diet, group behaviour therapy, stress management, or fiber intake, could easily be classified as conventional interventions rather than CAM. In addition, it was stated that CAMBRELLA, a large-scale project carried out on the use of CAM in 39 European Union countries, was consulted in the preparatory studies of the Regulation. However, CAMBRELLA found in its final report that research on CAM methods has several problems: "A literature review including 170 scientific papers identified the following key issues in CAM research: practical problems in CAM research (e.g. randomization, blinding), use of quantitative and qualitative research methods, research strategies/priorities, and issues related to specific modalities of CAM."¹³³ Another criterion taken into account by the Ministry of Health when creating the Regulation was FDA approval for that method.¹³¹ Yet the FDA did not approve some of the CAM methods legislated in Türkiye. Indeed, the FDA has issued many warnings for homeopathy, for example, and has stated that "Homeopathic products have not been approved by the FDA for any use and may not meet modern standards for safety, effectiveness, and quality".¹³⁴ In addition, the Science and Technology Committee of the UK Parliament House of Commons concluded that "there was no credible evidence of efficacy for homeopathy".¹³⁵ Nevertheless, those CAM methods were legalized in Türkiye despite the lack of evidence and lack of governmental approvals mentioned above. Under these

circumstances, it can be safely claimed that these policies legalizing 14 CAM modalities create a non-negligible risk to public health. Therefore, due to insufficient evidence on effectivity and safety, the mentioned CAM methods should not be applied unless further studies would show their both effectiveness and safety. Additionally, it should be remembered that the ethical principles of the profession, and the regulation of professional codes of ethics both national (The Statute of Medical Deontology) and international (World Medical Association Declaration of Geneva), supersede the "Regulation on Traditional and Complementary Medicine Practices" since professional ethics must always be antecedent to legal regulations.

Cochrane reviews are reported to have lower bias than non-Cochrane reviews¹³⁶⁻¹³⁸, hence we choose to incorporate them. Our widespread search for every practice led to involving every condition that was indexed in the Cochrane Database of Systematic Reviews; this is the main strength of this study. However, screening only one database creates a limitation, making it possible that we overlooked some evidence about several practices. Further studies with broader search strategies are necessary for a more robust comparison and more solid evidence on the effectiveness and safety of the CAM methods studied.

In conclusion, this systematic review has demonstrated that the level of evidence regarding the effectiveness and safety of Acupuncture, Apitherapy, Hypnotherapy, Leech therapy, Homeopathy, Cupping therapy, Chiropractic, Prolotherapy, Osteopathy, Maggot therapy, Mesotherapy, Music therapy, Reflexology, and Ozone therapy is insufficient

to be able to use them in daily medical practice. According to the GRADE system, further research is very unlikely to change the confidence in the estimate of effectiveness, which will only appreciably improve with high-quality evidence.⁴¹ Therefore, further studies aiming to produce high-quality evidence are needed to be able to make risk-benefit assessments scientifically and to validate the use of these modalities clinically.

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Supplementary Table Characteristic of the included studies

Authors, year	N; total included trials	Indication	Intervention	Controls	Quality of Evidence	Main Outcomes	Adverse Events	AMSTAR-2
Smith, 2020	3960; 28	Pain management during labour	Acupuncture or acupressure	Placebo, no treatment or other non-pharmacological forms of pain management in labour	Low-Moderate	Acupuncture may make little or no difference to the intensity of pain felt by women when compared with sham acupuncture. Acupuncture may increase satisfaction with pain relief compared to sham acupuncture and probably reduces the use of pharmacological analgesia. Acupressure probably slightly reduces the intensity of pain during labour	N/A	Low

						compared with the combined control.		
Mu, 2020	8270; 33	Chronic nonspecific low back pain	Acupuncture	Sham intervention, no treatment, and usual care	Low	Acupuncture may not play a more clinically meaningful role than sham in relieving pain immediately after treatment or in improving quality of life in the short term, and acupuncture possibly did not improve back function compared to sham in the immediate term. However, acupuncture was more effective than no treatment in improving pain and	Pain, bruising, hematoma, bleeding, worsening of LBP, and pain other than LBP	Moderate

						function in the immediate term.		
Farrell, 2020	21; 1	Fatigue in inflammatory bowel disease	Electroacupuncture	Control and sham electroacupuncture	Low	The evidence suggests electroacupuncture may result in a large reduction in fatigue compared to control and sham electroacupuncture	No adverse events were reported	Moderate
Griffiths, 2021	1221; 9	Preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section	Acupressure/acupuncture	Placebo	Low	Acupressure may reduce intraoperative vomiting but it is uncertain whether it reduces postoperative nausea or postoperative vomiting	Uncertain	Moderate
Armour et al., 2018	277; 5	Premenstrual syndrome (PMS)	Acupuncture and acupressure	Sham acupuncture, no treatment	Low	Acupuncture may reduce mood-related and physical symptoms of PMS and improve	Limited evidence for safety of acupuncture and	Moderate

						quality of life (QOL) compared to sham acupuncture Very limited evidence about acupuncture vs. no treatment Acupressure may reduce the severity of PMS and improve QOL compared to sham acupressure	no data for acupressure	
Cheong et al., 2013	4544;20	Reproduction assistment	Acupuncture	Placebo needles, no treatment	Low	No benefit for improvement of live birth rate, ongoing or clinical pregnancy rate	No significant side effects	High
Kim et al.,2016	1787;24	Chronic kidney disease	Acupuncture, acupressure, ear acupressure, transcutaneous electrical	Routine care	Very low	Manual acupressure increases fatigue, depression, sleep disturbance and uraemic pruritus in haemodialysis patients	No serious adverse events	Moderate

			acupuncture point stimulation, far-infrared radiation on acupuncture points and indirect moxibustion					
Cheng et al., 2017	531;6	Acute hordeolum	Acupuncture	Sham acupuncture, no treatment, other active treatments	Low	Acupuncture plus conventional treatments may be more beneficial for resolution or relief of acute hordeolum compared with conventional treatments only	Limited/ no data	Moderate
Wong et al., 2013	294;4	Traumatic brain injury	Acupuncture	No treatment, placebo, sham	Low	After acute TBI and in the rehabilitation phase acupuncture might improve overall func-	No serious adverse events	Moderate

				acupunctur e		tional outcome and motor and speech functions		
Xu et al., 2018	3946; 33	Acute stroke	Acupuncture	Open control or sham acupunctur e	Very low - low	The effects of acupuncture in reducing death or dependency or improving neurological and movement scores at the end of follow-up, as seen in trials comparing acupuncture with any control, were not seen in trials comparing acupuncture with the more reliable control of sham acupuncture.	Minor adverse events	Moderate

Cheuk et al., 2011	390; 10	Autism spectrum disorders (ASD)	Needle acupuncture, needle acupuncture plus conventional treatment, acupressure plus conventional treatment	Sham acupuncture, conventional treatment	N/A	No difference in the primary outcome of core autistic features. There was no evidence that acupuncture was effective for the secondary outcome of communication and linguistic ability	Bleeding, crying due to fear or pain, irritability, sleep disturbance and increased hyperactivity.	Moderate
Smith et al., 2018	7104; 64	Depression	Acupuncture	No treatment, wait list, treatment as usual, control acupuncture, medication	Low	Acupuncture may moderately reduce the severity of depression by end of treatment (SMD -0.66, 95% CI -1.06 to -0.25). There was a small reduction in the severity of depression of 1.69 points on the Hamilton Depression Rating Scale	No differences between groups	Moderate

						by end of treatment (95% CI -3.33 to -0.05). Acupuncture may confer small benefit in reducing the severity of depression by end of treatment (SMD -0.23, 95% CI -0.40 to -0.05). It may be beneficial in reducing the severity of depression by end of treatment (SMD -1.15, 95% CI -1.63 to -0.66).		
Cheuk and Wong, 2014	1538; 17	Epilepsy	Acupuncture	No treatment, placebo treatment, sham treatment or Anti-epileptic drugs	Moderate	Needle acupuncture plus Chinese herbs compared to chinese herbs and needle acupuncture compared to phenytoin was not effective in reducing seizure frequency; compared with	No serious adverse events	Moderate

						<p>valproate, needle acupuncture plus valproate was not effective in achieving freedom from seizure. Compared with antiepileptic drugs, catgut implantation at acupoints plus antiepileptic drugs was not effective in achieving seizure freedom.</p>		
Yang et al., 2018	1744; 22	Hypertension	Acupuncture	No treatment, sham acupuncture or minimal acupuncture,	Low	There is no evidence for the sustained blood pressure (BP) lowering effect of acupuncture that is required for the management of chronically elevated BP.	Pain sensation during needle insertion and small spot-bleeding, hypertensive emergency	Moderate

				antihypertensive drugs				
Shen et al., 2014	2875; 30	Schizophrenia	Acupuncture manipulation, moxibustion, electroacupuncture, acupoint injection, laser acupuncture, acupoint catgut treatment and electric acupuncture convulsive therapy	Anti-psychotic drugs, Traditional Chinese Medicine drugs, Electroconvulsive therapy	Low	Acupuncture plus standard antipsychotic treatment vs. standard antipsychotic treatment was better in mental health findings and time in hospital. Relapse was less in acupuncture plus low dose antipsychotics compared to standard dose antipsychotic drugs	Adverse effects were less in acupuncture groups	Moderate
Wang et al., 2013	60; 1	Stress urinary incontinence	Electroacupuncture	Midodrine hydrochloride	Low	Cure rates were low and not statistically significantly different in acupuncture group.	No adverse events in the acupuncture group	Moderate

Yang et al., 2016	2257; 31	Stroke rehabilitation	Traditional or contemporary acupuncture	Placebo acupuncture, sham acupuncture, or other conventional treatment.	Low	Acupuncture had beneficial effects on the improvement of dependency, global neurological deficiency, cognitive function, depression, swallowing function, swallowing function.	No serious adverse events	Moderate
Linde et al., 2018	4985;22	Prevention of episodic migraine	Acupuncture	No acupuncture, sham acupuncture, prophylactic drug treatment	Moderate	Acupuncture was associated with a moderate reduction of headache frequency over no acupuncture after treatment (four trials, 2199 participants; standardised mean difference (SMD) -0.56; 95% CI -0.65 to -0.48). Both after treatment (12 trials, 1646	Compared to drug prophylaxis fewer participants dropped out due adverse effects or reported adverse effects.	Moderate

						<p>participants) and at follow-up (10 trials, 1534 participants), acupuncture was associated with a small but statistically significant frequency reduction over sham. Acupuncture reduced migraine frequency significantly more than drug prophylaxis after treatment.</p>		
Linde et al. 2016	2349; 12	Prevention of tension-type headache	Acupuncture	Routine care or treatment of acute headaches, sham acupuncture, physiother	Moderate	<p>The proportion of participants experiencing at least 50% reduction of headache frequency was much higher in groups receiving acupuncture than in control groups. Among</p>	<p>Three trials reported the number of participants reporting adverse effects: 29 of 174 (17%) with acupuncture versus 12 of 103</p>	Moderate

				apy, massage or exercise		participants receiving acupuncture, 205 of 391 (51%) had at least 50% reduction of headache frequency compared to 133 of 312 (43%) in the sham group after treatment.	with sham (12%; odds ratio (OR) 1.3; 95% CI 0.60 to 2.7; low quality evidence)	
Deare et al., 2013	395; 9	Fibromyalgia	Electro- acupuncture (EA) and manual acupuncture (MA)	Sham/fake/ placebo acupunctur e, other types of placebo control, non- acupunctur e treatment, different styles of acupunctur	Low- Moderate	Low quality evidence from one study showed EA improved symptoms with no adverse events at one month following treatment. Moderate quality evidence from six studies indicated that EA or MA was no better than sham acupuncture. Moderate quality evidence from one study showed that adjunct acupuncture	No serious adverse events	High

				e or other treatment		therapy reduced pain compared with standard therapy alone (antidepressants and exercise). Low quality evidence from one study showed a short-term benefit of acupuncture over antidepressants in pain relief. Four studies reported no differences between acupuncture and control or other treatments.		
Gates 2006	1433; 7	Cocaine dependence	Auricular acupuncture	Sham acupuncture or no acupuncture	Low	No differences between acupuncture and sham acupuncture were found for attrition RR 1.05 (95% CI 0.89 to 1.23) or no	Not reported by any study	Moderate

						acupuncture: RR 1.06 (95%CI 0.90 to 1.2)		
Coyle 2012	1346; 8	Breech presentation	Moxibustion alone or in combination with acupuncture or postural techniques	No treatment, acupuncture, only moxibustion, only postural technique	Moderate	Moxibustion was not found to reduce the number of non-cephalic presentations at birth compared with no treatment (P = 0.45). Moxibustion resulted in decreased use of oxytocin before or during labour for women who had vaginal deliveries compared with no treatment (RR= 0.28, 95% CI= 0.13 to 0.60). Moxibustion was found to result in fewer non-cephalic presentations at birth compared with acupuncture (RR 0.25,	Unpleasant odour (with or without throat irritation), nausea and abdominal pain from contractions	Moderate

						95% CI 0.09 to 0.72). When combined with acupuncture, moxibustion resulted in fewer non-cephalic presentations at birth (RR 0.73, 95% CI 0.57 to 0.94), and fewer births by caesarean section (RR 0.79, 95% CI 0.64 to 0.98).		
Huang et al., 2011	2334; 24	Nocturnal enuresis	Acupuncture	No treatment or placebo or another treatment	Low	Acupuncture had better results than sham control acupuncture (RR for failure or relapse after stopping treatment 0.67, 95% CI 0.48 to 0.94) in a trial.	No data	Moderate
Brown et al., 2014	67; 1	Endometriosis	Acupuncture	Chinese herbal medicine	Low	Auricular acupuncture was significantly more effective at reducing pain associated with	No data	Overview of systematic reviews

						endometriosis than Chinese herbal medicine (RR 3.04, 95% CI 1.65 to 5.62,		
Nagraj et al., 2017	37; 1	Taste disturbances	Acupuncture	Sham acupuncture	Low	The acupuncture group showed improvement in taste discrimination (MD 2.80, 95% CI -1.18 to 6.78)	No adverse effects	High
Liddle and Pennick, 2015	118; 2	Low-back and pelvic pain during pregnancy	Acupuncture + usual prenatal care	Sham acupuncture + usual prenatal care	Low	All women reported pain relief and improved functional disability, but those in the ear acupuncture group reported significantly more pain relief and functional improvement than those in either the sham ear acupuncture or control group	No data	High

Furness et al., 2013	153;5	Dry mouth following radiotherapy treatment	Acupuncture	Sham acupuncture (placebo)	Low	No difference between acupuncture and control groups in dry mouth symptoms	Mild and temporary side effects	Moderate
Boelig et al., 2016	353;5	Hyperemesis gravidarum	Acupuncture, P6 Acupressure	Placebo, metoclopramide, phenobarbital, Chinese medicine	Low	No primary outcome data were available when acupuncture was compared with placebo. There was insufficient evidence to identify clear differences between acupuncture and metoclopramide. Acupuncture was more likely to have any effectiveness compared to phenobarbital and Chinese medicine.	No data	Moderate
Zhang et al., 2018	2569; 29	Side effects of chemotherapy or radiotherapy	Moxibustion, moxibustion	No treatment, conventional	Low	There were reductions in symptom scores for nausea and vomiting and	Most included studies provided no information	Moderate

			plus conventional treatment	treatment, sham moxibustio n,		diarrhoea, and higher mean white blood cell count serum haemoglobin and platelets when compared with sham moxibustion. Two studies showed moxibustion improved serumhaemoglobin concentrations compared with conventional medicines.	on the adverse effects.	
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Rada et al., 2010	139; 1	Hot flushes in women with a history of breast cancer	Acupuncture	Sham acupuncture	N/A	No differences between the different study groups were found for acupuncture or the treatment of hot flushes.	Minor adverse effects such as slight bleeding or bruising at the needle sit	Moderate
Boldt et al., 2014	47;2	Chronic pain in people with spinal cord injury	Acupuncture	Sham acupuncture, Trager treatment	NA	In two trials acupuncture was not superior to sham acupuncture or Trager treatment in reducing pain.	No adverse effects	Moderate

Manyande et al., 2015	67;1	Assisting the induction of anaesthesia	Parental acupuncture	Parental sham acupuncture	Low	The parent was less anxious, and the child was more co-operative, at induction of anaesthesia with parental acupuncture.	No data	Moderate
Franco et al., 2018	3290; 38	Chronic prostatitis/chronic pelvic pain syndrome	Acupuncture plus moxibustion, acupuncture, electroacupuncture+ advice+ exercise	Only acupuncture, sham acupuncture, advice+ exercise	Moderate	Acupuncture probably leads to clinically meaningful reduction in prostatitis symptoms compared with sham procedure (NIH-CPSI score -5.79, 95% CI -7.32 to -4.2).). Acupuncture may also lead to a clinically meaningful reduction in prostatitis symptoms compared with standard medical	No difference in adverse events	Moderate

						therapy (MD -6.05, 95% CI -7.87 to -4.24)		
Hurlow et al., 2012	88; 3	Cancer pain	TENS	Placebo, sham	N/A	There were no significant differences between groups.	Minor side effects	Moderate
Lee et al., 2015	7667; 59	Postoperative nausea and vomiting	Techniques intended to stimulate the PC6 acupoint: acupuncture, electro-acupuncture, laser acupuncture, transcutaneous electrical stimulation, conventional peripheral nerve stimulation, acu-	Sham treatment or drug therapy	Low-Moderate	There was a moderate-size effect in children and adults (PC6 acupoint stimulation versus sham); moderate-size effect on postoperative vomiting but not on postoperative nausea (PC6 acupoint stimulation and antiemetic versus antiemetic); no difference in the incidence of postoperative nausea and vomiting (PC6	Minor side effects, transient and self-limiting (e.g. skin irritation, blistering, redness and pain)	High

			stimulation device, acupressure, and capsicum plaster			acupoint stimulation versus antiemetic)		
Vogel et al., 2017	56;1	Labour induction	Acupuncture	Routine care	N/A	The intervention did not appear to have any impact on the number of women requiring additional agents to induce labour (RR 0.60, 95% CI 0.31 to 1.17) or having caesarean section (RR 0.43, 95% CI 0.17 to 1.11)	No data	Moderate
O'connor 2003	884; 21	Carpal tunnel syndrome	Laser acupuncture	Placebo	N/A	No significant difference in paraesthesiae or	No data	Moderate

						night pain was demonstrated between laser acupuncture and placebo over a three-week treatment period.		
Oduwole 2018	899; 6	Acute cough	Honey or honey+antibiotics	Honey-based cough syrup, non-honey cough syrup, placebo, no treatment, antibiotics alone or non-honey cough syrups+ antibiotics	Moderate	Honey probably reduces cough frequency better than no treatment or placebo (no treatment: meandifference (MD) - 1.05, 95% CI -1.48 to -0.62; I ² = 0%;placebo: MD -1.62, 95% CI -3.02 to -0.22; I ² = 0%). Honey may have a similar effect as dextromethorphan in reducing cough frequency (MD - 0.07,95% CI -1.07 to 0.94; I ² = 87%). Honey may be better than	No difference between honey and control groups	Moderate

						diphenhydramine reducing cough frequency (MD -0.57, 95% CI -0.90 to -0.24)		
Jull 2015	3011; 26	Topical treatment for wounds	Honey alone or in combination with other dressings or components	Dressings or other topical agent	Low	Burns treated with honey heal more quickly than those treated with silversulfadiazine (SSD) (WMD -5.12 days, 95%CI -9.51 to -0.73)	Unclear if there is a difference in rates of adverse events	Moderate
McCann 2010	786; 10	Preventing infectious complications in haemodialysis patients with	Topical honey ointment, Medihoney, Manuka honey	Antimicrobi al ointment, mupirocin ointment,	N/A	Topical honey did not reduce the risk of exit site infection (RR 0.45, 95%CI 0.10 to 2.11) or	Mild local skin discomfort	High

		central venous catheters		povidone-iodine ointment		catheter-related bacteraemia (RR 0.80, 95%CI 0.37 to 1.73).		
Norman 2017	576; 12	Pressure ulcers	Honey	Ethoxy-diaminoacridine plus nitrofurazone	Very low	No clear evidence of a difference between honey and the combination of nitrofurazone and ethoxy-diaminoacridine treatment (one trial) RR 11.42 (0.66 to 196.4)	No participant in either group experienced adverse systemic or local side effects directly attributed to treatment	Moderate
Norman 2016	886; 11	Surgical wounds	Honey-soaked gauze	EUSOL-soaked gauze	Moderate	One small study (N=43) showed that more open wounds resulting from excision of pyomyositis abscesses healed when treated with a honey-soaked gauze compared with a EUSOL-soaked gauze over three weeks'	No data	Moderate

						follow-up (RR: 1.58, 95% CI 1.03 to 2.42).		
O'Meara 2014	4486; 45	Venous leg ulcers	Manuka honey , alcium alginate dressing impregnated with Manuka honey	Hydrogel therapy, usual care, with dressings applied according to district nurse choice	N/A	no between-group difference in time to healing or complete healing was detected for honey-based productswhen compared with usual care	No difference between groups	Moderate

Norman 2017	5807; 56	Burns	Honey or honey-based dressings	Topical antibiotic	Moderate- High	Honey reduces time to healing compared with topical antibiotics: HR 2.45 (95% CI 1.71 to 3.52; I ² =66%). Honey results shorter mean time to healing compared with the non- antibacterial dressings (95% CI -6.30 to -4.34; I ² = 71%).	It is uncertain whether the incidence of adverse events differs between groups (very low certainty evidence)	Moderate
Cao 2015	3227;35	Acne vulgaris	Cosmetics with purified bee venom	Only cosmetics	Low	In one trial with 12 participants, purified bee venom was found to be statistically significantly better than the no PBV control when the post- treatment Korean Acne	No data	Moderate

						Grading System (KAGS) scores were measured, which were based on the number of lesions (MD -1.17, 95% CI -2.06 to -0.28, P = 0.01)		
Eekhof 2012	2826; 24	Ingrowing toenails	Manuka honey	Paraffin-impregnated tulle gras	N/A	No significant difference in postoperative pain between manuka honey dressing compared to paraffin-impregnated tulle gras (MD 0.03, 95% CI -0.47 to 0.53)	No data	Moderate
Worthington 2011	10,514; 131	Preventing oral mucositis for patients with cancer receiving treatment	Honey	No treatment	Low	Honey may be beneficial in the prevention of any mucositis (RR = 0.70, 85% CI 0.56 to 0.88, P = 0.002),	No data	High

						<p>moderate to severe mucositis (RR = 0.48, 95% CI 0.31 to 0.74, P = 0.0009) and severe mucositis (RR = 0.26, 95% CI 0.13 to 0.52, P = 0.0002)</p>		
<p>Adderley 2014</p>	<p>164; 4</p>	<p>Fungating wounds</p>	<p>Manuka honey-coated dressings</p>	<p>Silver-coated dressings</p>	<p>N/A</p>	<p>The median decrease in wound size in Group A (honey-coated dressings) was 15 cm² compared with 8 cm² in Group B (silver-coated dressings). This difference was not statistically significant (p = 0.563). There was no significant reduction in wound size for all patients (p = 0.388)</p>	<p>No data</p>	<p>Moderate</p>

Zimpel, 2020	153;3	Post-caesarean pain	Music plus analgesia	Placebo plus analgesia	Low	Music plus analgesia may reduce pain when compared with placebo plus analgesia at one hour and 24 hours; also when compared with analgesia at one hour and 24 hours.	Uncertain	Low
Sinha 2011	182; 7	Autism spectrum disorders	Auditory integration therapy (AIT) and other sound therapies that involved listening to music modified by filtering and modulation	Waiting list or receive no treatment, usual therapy or a placebo equivalent.	N/A	Studies did not demonstrate any benefit of auditory integration therapy over control conditions.	No significant differences were found between groups	Low

Galaal 2011	1102; 6	Reducing anxiety in women undergoing colposcopy	Listening to music during colposcopy	Usual care	Low	Music during colposcopy significantly reduced anxiety levels (MD = -4.80, 95% CI: -7.86 to -1.74) and pain experienced during the procedure (MD = -1.71, 95% CI: -2.37 to -1.05) compared to not listening to music.	No adverse events reported	Moderate
Laopaiboo n 2009	76; 1	Improving maternal and infant outcomes in C/S	Standard care plus at least 30 minutes listening to music through earphones via a compact disc player	Received standard care and no music	Low	Music added to standard care during caesarean section under regional anaesthesia had some impact on pulse rate at the end of maternal contact with the neonate in the intra-operative period (MD -7.50 fewer beats per minute, 95% CI -14.08 to -0.92) and	No data	Moderate

						after completion of skin suture for the caesarean section (MD -7.37 fewer beats per minute, 95% CI -13.37 to -1.37).		
Jespersen 2015	314;6	Insomnia	Listening to music	No treatment or treatment-as-usual	Moderate	The results of a random-effects meta-analysis revealed an effect in favour of music listening (mean difference (MD) -2.80; 95% confidence interval (CI) -3.42 to -2.17; Z = 8.77, P < 0.00001)	No adverse events reported	High
Bradt 2013	1369;26	Anxiety reduction in coronary heartdisease patients	Listening to music, singing, playing music	Usual care	Low	Music interventions have a small beneficial effect on psychological distress and anxiety in people with CHD and this effect is inconsistent across studies (MD = -	No adverse events reported	Moderate

					<p>1.26, 95% CI -2.30 to -0.22, P = 0.02, I² = 0%).</p> <p>listening to music reduces heart rate (MD = -3.40, 95% CI -6.12 to -0.69, P = 0.01), respiratory rate (MD = -2.50, 95% CI -3.61 to -1.39, P < 0.00001) and systolic blood pressure (MD = -5.52 mmHg, 95% CI -7.43 to -3.60, P < 0.00001). The results also suggest that listening to music may improve patients' quality of sleep following a cardiac procedure or surgery (SMD = 0.91, 95% CI 0.03 to 1.79, P = 0.04).</p>	
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Magee 2017	775;29	Acquired brain injury	Playing musical instruments, Singing and music-based voice interventions, RAS or rhythmic auditory cueing (RAC), Receptive interventions in which participants listen to Music, Songwriting	Standard care alone, standard care with placebo, standard care combined with other therapies	Low	Rhythmic auditory stimulation may be beneficial for improving the following gait parameters after stroke. There were an increase in gait velocity of 11.34 metres per minute (95% confidence interval (CI) 8.40 to 14.28; 9 trials; 268 participants; P < 0.00001; moderate- quality evidence). Music interventions may be beneficial for improving the timing of upper extremity function after stroke. (95% CI -1.69 to -0.47; 2 trials; 122 participants; very low- quality evidence). Music	No data	High
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						<p>interventions may be beneficial for communication outcomes in people with aphasia following stroke. Overall, communication improved by 0.75 standard deviations in the intervention group, a moderate effect (95% CI 0.11 to 1.39; 3 trials; 67 participants; P = 0.02; very low-quality evidence).</p>		
Bradt 2016	3731; 52	Improving psychological and physical outcomes in cancer patients	Music therapy interventions offered by trained music therapists; music medicine	Standart care, placebo	Low	There were average anxiety reduction of 8.54 units (95% confidence interval (CI) -12.04 to -5.05, P < 0.0001) on the Spielberg State	No adverse events reported	High

			interventions (listening to pre-recorded music, offered by medical staff)			Anxiety Inventory; positive impact on depression (standardized mean difference (SMD):-0.40, 95% CI-0.74 to-0.06, P = 0.02). The results suggest a large effect of music interventions on patients' quality of life (QoL) and fatigue.		
Bradt 2014	805; 14	Mechanically ventilated patients	Music listening	Standart care	Low	Music listening resulted, anxiety reduction (95% CI -1.75 to -0.47, P = 0.0006). Also reduced respiratory rate and systolic blood pressure.	No adverse events identified	High
Bradt 2013	2051; 26	Preoperative anxiety	Listening to pre-recorded music	Standart care	Low	Music listening resulted, on average, in an anxiety reduction (95% CI -7.27 to -4.17, P < 0.00001)	No adverse events identified	Moderate

Aalbers 2017	421; 9	Depression	Any form of music therapy (e.g. improvisational, re-creative, compositional, or receptive methods) provided alone or in addition to TAU	Treatment as usual (TAU), psychological therapies, pharmacological therapies, other therapies,	Low-Moderate	There were less clinician-rated depressive symptoms (SMD -0.98, 95% CI -1.69 to -0.27, 3 RCTs, 1 CCT, n = 219) and patient-reported depressive symptoms (SMD -0.85, 95% CI -1.37 to -0.34, 3 RCTs, 1 CCT, n = 142) in music therapy and TAU groups vs TAU groups.	Music therapy plus TAU is not associated with more or fewer adverse events than TAU alone	Moderate
Geretsegger 2016	165; 10	Autism spectrum disorder	Music therapy delivered by a professional music therapist	No-treatment, or standard care	Moderate	Music therapy was superior to 'placebo' therapy or standard care with respect to the primary outcomes social interaction within the therapy context (SMD 1.06, 95% CI 0.02	No adverse events reported	Moderate

						<p>- 2.10); generalised social interaction outside of the therapy context (SMD 0.71, 95% CI 0.18- 1.25), non-verbal communicative skills within the therapy context (SMD 0.57, 95% CI 0.29-0.85), verbal communicative skills (SMD 0.33, 95% CI 0.16 - 0.49), initiating behaviour (SMD 0.73, 95% CI 0.36-1.11), and social-emotional reciprocity (SMD 2.28, 95% CI 0.73 to 3.83)</p>		
Geretsegger 2017	1215; 18	Schizophrenia and schizophrenia-like disorders	Music therapy or music therapy added to standard care	Placebo, standard care or no treatment	Low-Moderate	A positive effect on global state was found for music therapy compared to standard care (RR 0.38	No data	Moderate

						95% CI 0.24 to 0.59)		
Van der Steen	1097; 22	Dementia	Music-based therapeutic interventions	Usual care or other activities	Low-Moderate	Interventions may improve emotional well-being and quality of life (standardised mean difference (SMD) 0.32, 95% confidence interval (CI) 0.02 to 0.62) and reduce anxiety (SMD -0.43, 95% CI -0.72 to -0.14), reduce depressive symptoms (SMD -0.27, 95% CI -0.45 to -0.09) and overall behaviour problems (SMD -0.23, 95% CI -0.46 to -0.01).	No adverse events reported	Low
Fleming 2016	931; 14	Alleviating pain during orthodontic treatment	Brain wave music (BWM) or cognitive behavioural therapy	No special instructions	Very low	One study showed there was less pain at 24 hours (MD -26.65 mm, 95% CI -39.06 to -	Not measured	High

						14.24; P < 0.001) and three days (MD -23.44 mm, 95% CI -36.82 to -10.06; P < 0.001) in brain wave music group compared to controls		
Hu, 2015	1569; 30	Sleep promotion in the intensive care unit	Earplug-delivered sleep-inducing music, 45-minute music-listening intervention, use of earplugs and eye masks with music listening, 20-minute relaxing music therapy,	No music, but earplugs and eye shield worn, usual care without music, no use of earplugs or eye masks and no music, sitting	Very low	participants in the music group had shorter stage two sleep time (P value = 0.014) and longer stage three sleep time (P value = 0.008). significantly greater reduction in BIS in the music intervention group (post-test mean = 81, SD = 10) compared with the control group (post-test mean = 94, SD	No data	Moderate

			individualized music intervention	and uninterrupted resting		= 5) (P value < 0.01).		
Smith, 2018	1731; 15	Pain management in labour	Relaxation, music and guided imagery; relaxation and music; music; massage and relaxation or music and relaxation; compared music and breathing techniques	Usual care, breathing techniques	Low	There was evidence of lower pain intensity in the latent phase for women receiving music (MD -0.73, 95% CI -1.01 to -0.45). No clear benefit in the active phase (MD -0.51, 95% CI -1.10 to 0.07), no clear benefit in terms of reducing assisted vaginal birth (RR 0.41, 95% CI 0.08 to 2.05) or caesarean section rate (RR 0.78, 95% CI 0.36 to 1.70).	No data	High
McNamara, 2017	112; 3	Chronic obstructive	Singing	Film workshop,	Low	There was a statistically significant improvement	No adverse events or side	High

		pulmonary disease		handcraft work, and no intervention		in the SF-36 Physical Component Summary (PCS) score favouring the singing group (MD 12.64, 95% CI 5.50 to 19.77). No difference in dyspnoea or respiratory-specific quality of life.	effects were reported	
Huang 2011	2334; 24	Nocturnal enuresis in children	Hypnosis	No treatment or placebo or another treatment	Low	One trial suggested hypnosis was better than imipramine in the treatment of enuresis. Another trial claimed that children receiving trance or suggestions or a combination of trance and suggestions had better outcomes than waiting list controls. And in one trial, hypnotherapy appeared	Not reported	Moderate

						to have a higher failure rate than alarm therapy.		
Soares-Weiser 2018	1278; 31	Antipsychotic-induced tardive dyskinesia	Hypnosis or relaxation (8 sessions)	Treatment as usual	Very low	One trial showed (N=15) a benefit in favour of hypnosis or relaxation when compared to TAU in clinic improvement (RR 0.45, 95% CI 0.21 to 0.94). But hypnosis was no better compared to relaxation (RR 0.11, 95% CI 0.01 to 1.64)	Not reported	Moderate
Boldt 2014	616;16	Chronic pain in people with spinal cord injury	Self-hypnosis	Electromyography biofeedback relaxation training	N/A	No evidence about self-hypnosis reduces chronic pain	No data	Moderate
Birnie 2018	5550;59	Needle-related procedural pain and distress	Hypnosis	Standard care control	Very low	Hypnosis was efficacious for reducing self-reported pain (n = 5, 176 participants; SMD -1.40, 95% CI	No adverse effect reported	High

						-2.32 to -0.48) and distress (n = 5, 176 participants; SMD -2.53, 95% CI -3.93 to -1.12), and behavioral distress (n = 6, 193 participants; SMD -1.15, 95% CI -1.76 to -0.53), but not behavioral pain (n = 2, 69 participants; SMD -0.38, 95% CI -1.57 to 0.81)		
Abbott 2017	928;18	Recurrent abdominal pain in childhood	hypnotherapy , guided imagery	usual care, wait-list	Low	There were evidence of greater treatment success post-intervention (OR 6.78, 95% CI 2.41 to 19.07; Z = 3.63; P = 0.0003) as well as reductions in pain intensity (SMD -1.01, 95% CI -1.41 to -	No adverse effect reported	High

						0.61; Z = 4.97; P < 0.00001) and pain frequency (SMD -1.28, 95% CI -1.84 to -0.72; Z = 4.48; P < 0.00001)		
Hondras 2005	156;3	Asthma	Chiropractic spinal manipulation	Sham manoeuvre	Moderate	In children there were no significant differences between the groups in the degree of peak expiratory flow change from baseline. In adults with chronic asthma there were no significant differences between the groups in self-rated asthma, lung function, or beta-agonist spray use.	No side-effects were reported	Moderate

Huang 2011	2334; 24	Nocturnal enuresis in children	Chiropractic	No treatment or placebo or another treatment	Low	Active chiropractic adjustment had better results than sham adjustment (RR for failure to improve 0.76, 95% CI 0.60 to 0.95)	Headache, stiff neck and lumbar spine pain in Chiropractic group	Moderate
Rubinstein 2011	6070;26	Chronic low-back pain	Spinal manipulative therapy (SMT)	Inert interventions, sham SMT, all other interventions	Low-High	SMT has a small, statistically significant but not clinically relevant, short-term effect on pain relief (MD: -4.16, 95% CI -6.97 to -1.36) and functional status (SMD: -0.22, 95% CI -0.36 to -0.07) compared to other interventions. There is very low quality evidence that SMT is not statistically significantly	Muscle soreness, stiffness, and/or transient increase in pain. No serious complications.	High

						more effective than inert interventions or sham SMT for short-term pain relief or functional status.		
Rubinstein 2012	2674; 20	Acute low-back pain	Spinal manipulative therapy (SMT)	Inert interventions, sham SMT, all other interventions	Low	No difference in effect of SMT compared to inert interventions, shamSMT, or when added to another intervention	No serious adverse events	High
Proctor 2006		Dysmenorrhoea	High velocity, low amplitude (HVLA) spinal manipulative treatment The Toftness technique ('low-force' chiropractic technique)	Sham manipulation	N/A	One trial indicated a significant difference between active and sham treatment in favour of HVLA manipulation (MD -1.41, 95% CI -2.55 to -0.27). Another one showed	No significant differences in the adverse effects between groups	Moderate

						<p>that pain scores for the HVLA treatment group had not dropped. After three months treatment the sham manipulation participants had significantly lower pain scores (MD 2.20, 95% CI 1.38 to 3.02), however at the six-month follow up there was a significant difference in favour of the Toftness manipulation group (MD -1.40, 95% CI -2.21 to -0.59) significantly more than for the sham treatment group after one</p>		
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						treatment in one cycle (MD 2.08, 95% CI -3.20 to 7.36).		
Sinopoulou , 2021	30;1	Management of abdominal pain in Crohn's disease and inflammatory bowel disease	Soft non-manipulative osteopathic treatment	No intervention	Very low	There was no clear difference in pain intensity in the osteopathic group when compared to the no-intervention group (MD 0.01, 95% CI -1.81 to 1.83).	N/A	Moderate
Yang 2013	434;6	Pneumonia	Osteopathic manipulative treatment plus routine treatment	Placebo plus routine treatment	Low	Osteopathic manipulative treatment (versus placebo) did not increase the cure rate or chest X-ray improvement rate. Osteopathic manipulative treatment reduced the mean duration of hospital stay by 2.0 days	One trial reported that transient muscle tenderness emerged after treatment in two individuals	Moderate

						(mean difference (MD) - 2.0 days, 95% CI -3.5 to -0.6). It reduced the duration of intravenous (MD -2.1 days, 95% CI - 3.4 to -0.9) and total antibiotic treatment (MD -1.9 days, 95% CI - 3.1 to -0.7).		
Liddle 2015	5121;34	Preventing and treating low-back and pelvic pain during pregnancy	Usual prenatal care plus osteopathic treatments in 2-week intervals; usual obstetric care plus Osteomaniplative Therapy	Usual prenatal care plus osteopathic treatments after an 8-week untreated waiting period; usual obstetric care plus	Moderate	OMT added to usual prenatal care improved pain (effect size -7.11; 95% CI - 10.30 to -3.93) and functional disability (effect size -2.25; 95% CI -3.18 to -1.32) significantly more than usual prenatal care alone, but not more than usual prenatal care plus	No adverse effects	Moderate

				sham ultrasound		placebo ultrasound (From one study, N=400). OMT significantly reduced pain (68% improvement versus 0%; P < 0.0005) and improved functional disability (28% improvement versus 20% deterioration) over those on a waiting list (From one study, N=57).		
Hawke 2018	1562; 8	Preventing and treating acute respiratory tract infections in children	Oral homeopathic medicinal product	Standard treatments or identical oral placebo	Low	There were no benefit of homeopathic medicinal products compared to placebo on ARTI recurrence or cure rates in children (For prevention OR 1.14, 95% CI 0.83 to 1.57;	Increase in the occurrence of non-severe adverse events in the treatment group	Moderate

						Short-term cure OR 1.31 favouring placebo, 95% CI 0.09 to 19.54; Long-term cure OR 0.99, 95% CI 0.10 to 9.67)		
McCarney 2004	556; 6	Chronic asthma	Homeopathic dilutions, isopathy	Placebo as adjunctive treatment to usual care	N/A	No trial reported a significant difference on validated symptom scales. There were conflicting results in terms of lung function between the studies.	No serious adverse events	Moderate
Smith 2003	133; 2	Induction of labour	Caulophyllum tablets	Placebo	N/A	There were no differences seen in any of the primary outcome measures	No data	Low
van der Wouden 2017	1650; 22	Cutaneous molluscum contagiosum	Homoeopathic drug calcarea carbonica	Plain sugar globules as a placebo	Low	Homeopathic calcarea carbonica appears to be more effective than	No adverse effects reported	High

						placebo (1 study, 20 participants, RR 5.57, 95% CI 0.93 to 33.54)		
Rada 2010	1373; 16	Hot flushes in women with a history of breast cancer	Single homeopathic remedy, Combination homeopathic remedy (Hyland's menopause), tablet, granule or liquid form homeopathic medicines	Identical-appearing placebo	N/A	There were no significant effects observed in a fouritem profile score that included two self-rated symptom items, an activity of daily living item and a general feeling of well-being item (mean difference -0.10; 95% CI -4.86 to 4.66). There were no statistical differences among comparisons for the frequency or severity score of hot flushes.	No differences between groups	Low

Cao, 2016	3227; 35	Acne vulgaris	Wet cupping, wet-cupping therapy and herbal decoction, wet-cupping therapy and acupuncture, wet-cupping therapy combined with herbal medicinal mask, wet cupping, acupuncture, and massage as intervention therapy	Tetracycline, herbal decoction, minocycline, vitamin A acid, viaminate capsule, zinc gluconate oral liquid	Low	One trial compared individualised herbal decoction plus wet-cupping therapy with wet-cupping therapy, found no difference (RR 2.33, 95% CI 0.67-8.18). One study compared wet-cupping therapy with externally applied viaminate cream, showed reduction in acne severity score but no difference in remission (RR 5.00, 95% CI 0.26-98.00). Two studies compared wet cupping to tetracycline showed significant remission (RR 2.50, 95% CI 1.31 to 4.77; RR 2.83, 95% CI 1.29 to	Black and blue spots on the skin	Moderate
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						<p>6.22). Six trials compared wet-cupping therapy plus acupuncture with western drugs. There were no difference in skin lesion scores and number of participants with remission. One study showed Acne quality of life score was better in cupping plus acupuncture vs. vitamin A cream. One trial showed no difference between wet-cupping therapy plus herbal medicinal mask and viaminate capsule for remission (RR 1.80, 95% CI 0.67 to 4.85). In a study compared wet-</p>		
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						cupping therapy, acupuncture, and massage, with zinc gluconate oral liquid; there was significant difference in 'Skin lesion scores' (MD -3.87, 95% CI -6.97 to -0.77); but no difference in remission (RR 4.13, 95% CI 1.00 to 17.04).		
Hough, 2008	106; 3	Reducing respiratory morbidity in infants requiring ventilatory support	Cupping	Contact heel percussion	N/A	There was an increase in the incidence of hypoxaemia and increase in oxygen requirement with cupping when compared to contact heel percussion	N/A	Moderate
Rueda 2011	1592; 15	Improving well-being and quality	Reflexology; 15 to 30-	No interventio	N/A	In one study pre-intervention anxiety	No data	Moderate

		of life in patients with lung cancer	minute teaching session on foot reflexology to the partner by a certified reflexologist, an optional 15 to 30-minute foot reflexology session for the partner, and a 30-minute, partner-delivered foot reflexology intervention for the patient	n, Usual care plus 30-minute reading session from their partners		scores were higher than pre-control time scores and anxiety scores were lower after the intervention than after the control time. The difference in score reduction between control and intervention groups was also significant. Another study showed patients in the reflexology group had 34% reduction in pain from baseline to post intervention compared with a reduction of 2% in controls;		
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Cramp 2013	11;1	Fatigue in rheumatoid arthritis	Reflexology massage	Non- specific foot massage	Low	The mean fatigue (Re- flexolgy) in the interven- tion groups was lower, but not sinificant. (SMD -1.24 (-2.59 to 0.11).	Not reported	Moderate
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