

The effectiveness of complementary and alternative medicine in the symptom management of pruritus in patients with end-stage kidney disease: a systematic review

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Abstract

Background Uraemic pruritus is a common symptom in end-stage kidney disease (ESKD) with a documented poor response to standard medical treatment. Patients seeking relief may self-medicate using complementary and alternative medicine (CAM), often without medical supervision. Healthcare professionals seeking to alleviate discomfort may be reluctant to promote CAM usage due to scant evidence on efficacy and effectiveness.

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Aim To systematically review the use of CAM for pruritus management in patients with ESKD.

Method MEDLINE, CINAHL EMBASE, Cochrane databases, grey literature and hand searches occurred using specific MeSH terms. Studies using CAM in the treatment of symptoms for ESKD patients experiencing pruritus were considered relevant. Articles available in English, written from 2000 and later were appraised using the Joanna Briggs Institute (JBI) critical appraisal tools.

Results 193 studies were screened as per the inclusion criteria. 21 studies were identified – 11 randomised controlled trials (RCTs), seven quasi-experimental, two case studies, and one cross-sectional. Interventions studied included acupressure, acupuncture, aromatherapy, homeopathy, music therapy, oral supplements, thermal therapy and topical application. Studies claiming consistent benefits were acupressure, acupuncture and aromatherapy.

Conclusion CAM encompasses multiple interventions with very few studies consistent in design and measurement, resulting in a gap in evidence on safety and effectiveness. Further research is needed incorporating standardised validated tools to establish best practice. CAM use should be discussed with patients and integrated into the health assessment process so that interventions can be safely monitored.

Introduction

Pruritus in patients with end-stage kidney disease (ESKD) presents a significant symptom burden, negatively impacting quality of life (Murtagh et al., 2007). Patients experiencing pruritus or uraemic itch often experience skin irritability and sensitivity, disrupted sleep patterns, reduced social functioning, subsequent depression (Sukul et al., 2019; Shirazian et al., 2016), and associated mortality (Simonsen et al., 2017). The prevalence of pruritus in patients with chronic kidney disease (CKD) at Stages 3, 4 and 5 who are not on dialysis, range from 24% (Sukul et al., 2019) to as high as 74% for those on the renal palliative care pathway (Shirazian et al., 2016). The underlying cause of uraemic pruritus is not fully understood and is thought to be multifactorial (Simonsen et al., 2017) with physiological factors such as hyperphosphataemia, iron deficiency anaemia, secondary hyperparathyroidism and chronic inflammation as possible pathophysiologic mechanisms (Akrami et al., 2016; Pakfetrat et al., 2013; Simonsen et al., 2017). Conventional treatments, including oral antihistamines, mast cell stabilisers and capsaicin, have been found to have varying efficacy (Simonsen et al., 2017). The use of gabapentin and pregabalin have been found to be effective. These drugs are excreted by the kidneys, so vigilant dose management is required in patients with ESKD to minimise the effects of drug accumulation which include drowsiness and dizziness (Malekmakan et al., 2018).

In an attempt to alleviate discomfort, complementary and alternative medicine (CAM) is seen as a popular and socially acceptable healthcare option. It is estimated that two out of three Australians use CAM and that the annual expenditure on CAM exceeds the spending on the Pharmaceutical Benefits Scheme (PBS) (von Conrady & Bonney, 2017). Significant drivers for the use of CAM in the general population are an “ageing population and increase in chronic disease”, as

well as a growing interest in promoting health and wellbeing (Complementary Medicines Australia [CMA], 2014, p.1). Amongst patients with ESKD, a recent study of dialysis patients in Trinidad indicated that CAM uptake was as high as 18.8%, with all CAM users reported to be unconcerned about medical supervision (Bahall, 2017). Another study of dialysis patients from India indicated that 26% of the dialysis population were using CAM (Rao, et al., 2016), whilst 36% of dialysis patients in the USA reported using CAM within the past month (Birdee et al., 2013). This follows the growing trend toward CAM use in the general population of the USA, reported as between 9–65% (Ernst, 2000). This growing popularity of CAM indicates that many patients are looking for relief of symptoms without using conventional medicine or medical supervision (Zare et al., 2018).

The World Health Organization (WHO) defines the terms complementary medicine, or alternative medicine as a “... broad set of health care practices that are not part of that country’s own tradition or conventional medicine and are not fully integrated into the dominant health-care system” (WHO, 2014, p. 15). However, this description does not provide a definitive list of therapies considered eligible as CAM, creating a challenge for researchers and reviewers who seek to develop inclusion/exclusion criteria. The Cochrane Collaboration have sought to develop an operational definition of CAM which... “tests whether a specific instance is or is not a member of the construct through a series of criteria or tests” (Weiland et al., 2011, p. 52). This includes the consideration of whether the context of the “therapy/condition pairing” was deemed as conventional medicine or CAM (Weiland et al., 2011, p. 53). Other considerations include the changing medical model, with therapies once considered CAM now seen as allopathic. In Australia, conventional therapy could be indicated by recommended best practice guidelines, the allocation

of a Medicare item number or a health fund rebate. For the purposes of this review, the research group decided to adopt an operational criterion that included CAM therapies that were practicable for the patient to access and safely administer without conventional medical supervision.

The aim of this systematic review is to identify the effectiveness of CAM in the management of pruritus for patients with ESKD. This review will inform health professionals regarding the evidence for safety and efficacy of CAM therapy options in treating uraemic pruritus.

Methods

Search strategy

A PICO (population, intervention, comparison and outcome) question was formulated as a guideline for the search strategy (Figure 1). A search was conducted using four electronic databases – Embase, CINAHL, Pubmed and the Cochrane Library. The following MeSH terms were used in the search strategy: Kidney Failure, Chronic; Renal Dialysis, Renal Insufficiency, Chronic; Peritoneal Dialysis, Renal Replacement Therapy, Pruritus, Complementary Therapies, Massage, Mind-Body Therapies, Biofeedback, Psychology, Aromatherapy, Hypnosis, Laughter Therapy, Meditation, Relaxation Therapy, Tai Ji, Therapeutic Touch, Yoga, Acupuncture, Acupuncture Therapy, Drugs, Chinese Herbal, Medicine, Chinese Traditional, Plant Extracts, Dietary Supplements, Music Therapy and Animal Assisted Therapy. Synonyms for these terms were also searched as in-text terms. These terms were used employing the Boolean operators “AND” or “OR” or combinations of both. Further searches were undertaken of databases including Google Scholar, Trial Registries and reference lists from systematic reviews.

The reviewers sought to review the effects of CAM on pruritus in ESKD. Initial searching of the internet and databases resulted in a total of 193 articles; a database search returned 129 articles and a further 64 were found via hand and internet searching. Of these, 38 were immediately excluded

as duplicates and a further 95 were excluded based on their abstracts. A total of 60 full articles were assessed for eligibility; 39 were excluded based on the inclusion criteria, and an additional 10 articles were identified from reference lists. A further 10 articles were excluded, with 21 articles critically appraised.

Inclusion and exclusion criteria

The inclusion criteria comprised of original research articles available in the English language, by a peer-reviewed journal, between January 2000 and January 2019, and in adults over the age of 18 years. Non English publications were included; however, if the full text article was not available in English then it was excluded. Peer reviewed trials studying the use of CAM in treating the symptoms of ESKD patients experiencing uraemic pruritus were considered relevant. Randomised controlled trials (RCTs), quasi-experimental trials, case-controlled studies, pilot and cross-sectional studies were also included.

A number of systematic reviews were identified during the search. While systematic reviews were not included in the search strategy, which was limited to original research, the reference lists of reviews were checked for relevant articles. A meta-analysis was not conducted due to the heterogeneous nature of the interventions and outcome reporting in the studies included. The 21 studies included reported on 16 different CAM. While four studies did look at acupressure, the specific nature of how that acupressure was conducted, using different techniques and pressure points for each study, prohibited useful data aggregation. Studies looking at the impact of aromatherapy and acupuncture were unable to be compared due to significant variations in data collection and outcome measures. Visual analog scale (VAS) (9 studies) and pruritus scores (6 studies) were the most commonly reported outcomes; however, the way that this data was measured and collected differed markedly from study to study.

Studies were excluded for CAM where a medical doctor's prescription or referral was required. Studies on animals were excluded, along with articles that were not translated into English. Studies including CAM and pruritus outside the context of ESKD were also excluded.

Critical appraisal

Thirty-one articles were critically appraised by two independent reviewers using the Joanna Briggs Institute (JBI) critical appraisal checklists for RCTs, cohort studies, quasi-experimental, case studies, pilot and cross-sectional studies (Johanna Briggs Institute, 2017). If disagreement arose, the research team sought additional support from a third reviewer to achieve resolution. As a result, 21 studies were accepted for review.

A flow diagram of the selection procedure was constructed using the preferred reporting items for systematic review and

Figure 1 - PICO question

Population	Patients with end-stage kidney disease (ESKD) +/- dialysis therapy experiencing pruritus
Intervention	Complementary and alternative medicine (CAM)
Comparison	Use of CAM with standard medical therapy vs standard medical therapy alone
Outcome	Statistically significant reduction in pruritus symptoms following CAM intervention
Question	Is CAM effective in the symptom management of pruritus in patients with ESKD?

meta-analyses (PRISMA) methodology (Moher, 2009) as a guide (Figure 2).

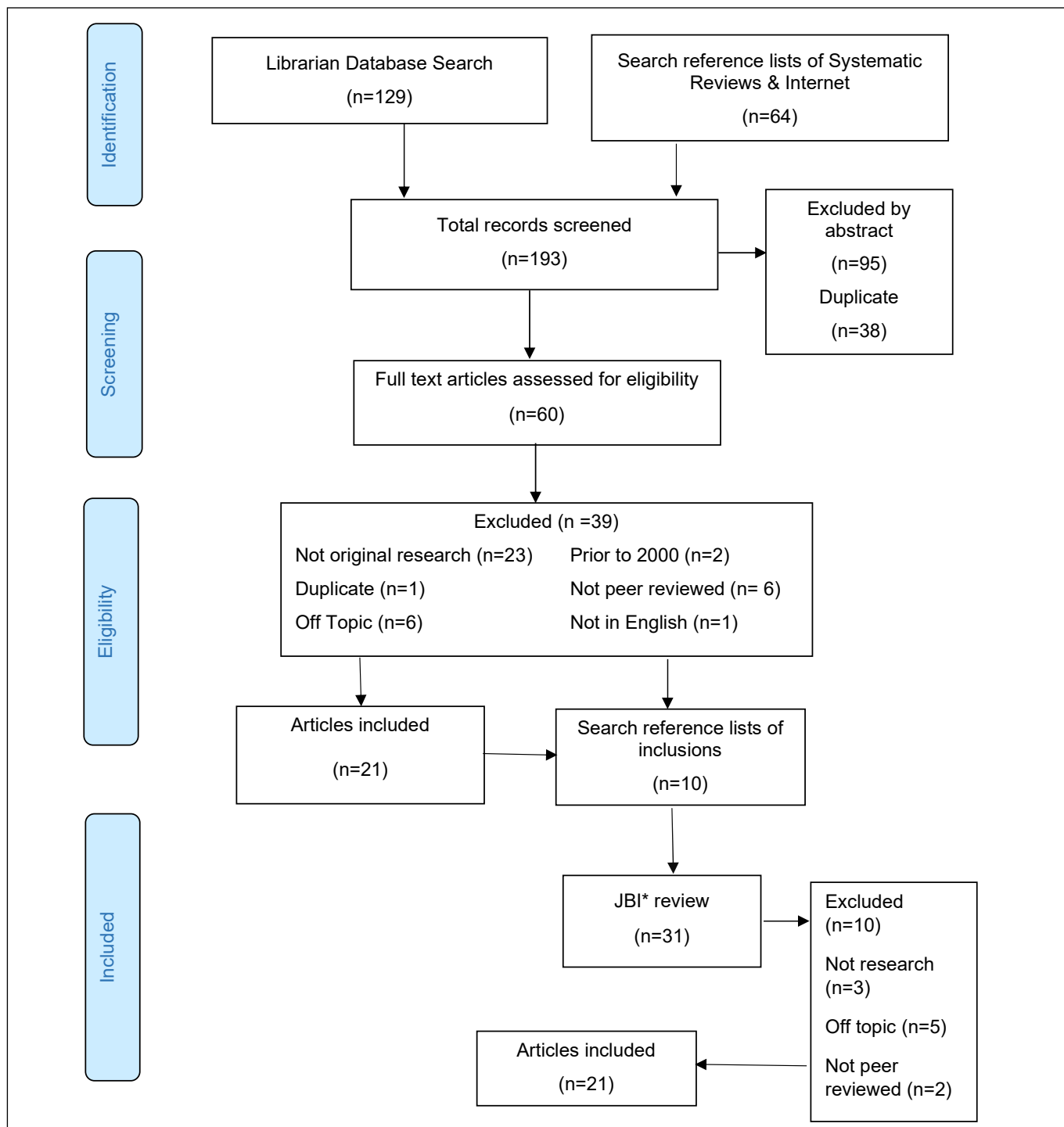
Risk of bias

The reviewers sought to assess the quality of each study along with risk of bias. Two different risk of bias tools were used depending on study type – the revised Cochrane risk of bias tool for randomised trials (ROB2) (Higgins et al., 2016) and the Newcastle Ottawa scale (NOS) tool for quasi-

experimental and cohort trials (Wells et al., 2011). Each RCT study was reviewed according to the specific ROB2 criteria and associated algorithm with scoring as follows: *low* risk of bias for all domains; *some concern* in one domain, but overall low risk of bias; or *high* risk of bias for studies with multiple domains of concern. The outcome has been summarised in Table 1.

The NOS tool measured the quality of quasi-experimental studies across a different set of criteria, with resultant studies

Figure 2. Flow diagram of selection procedure



*Johanna Briggs Institute
PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) 2009

based on a star rating. “The scale evaluates the domains of selection, comparability and outcome or exposure. One star allocated for each feature of quality present, to a maximum of nine (the comparability domain can score up to two stars). No specific value is assigned to high or low quality, although higher scores indicate greater use of favourable methodological aspects” (Harrison et al., 2017, p. 361). Table 2 indicates the authors’ opinion on the quality of study based on the NOS tool.

Data synthesis

The studies were synthesised into a table including: author; year and country; study design and sample size; data collection method; statistical significance between treatments; limitations/adverse reactions and risk of bias – ROB2 or NOS. The information was then organised into CAM intervention groups within the table (Table 3).

Among the 11 RCTs only two studies achieved all the criteria for the JBI RCT critical appraisal checklist (Chen et al., 2006; Pakfetrat et al., 2014). Five were unclear about how

Table 1. Risk of bias for RCTs

Author	ROB2*
Jedras et al. (2003)	low
Kilic Akca & Tasci (2016)	low
Yan et al. (2015)	low
Chou et al. (2005)	low
Burrai et al. (2014)	low
Akrami et al. (2016)	low
Begum et al. (2004)	low
Pakefetrat et al. (2014)	low
Hsu et al. (2009)	low
Chen et al. (2006)	low
Cavalcanti et al. (2003)	high

* Revised Cochrane risk of bias tool (Higgins et al., 2016).

Table 2. Quality of study assessment for non-randomised studies

Author	NOS*
Lin et al. (2011)	*****
Zare et al. (2018)	*****
Ristic-Medic et al. (2014)	*****
Cürcani & Tan (2014)	*****
Kilic Akca et al. (2013)	*****
Okada & Matsumoto (2004)	*****
Szepietowski et al. (2004)	*****
Ro et al. (2002)	*****
Weishaar et al. (2005)	****
Gao et al. (2002)	****

* Newcastle Ottawa scale tool (Wells et al., 2011).

participants were randomised (Akrami et al., 2016; Begum et al., 2005; Cavalcanti et al., 2003; Chou et al., 2005; Jedras et al., 2005). Nine studies indicated that either the participants, those delivering treatment, or the outcome assessors were not blind to the treatment assignment (Akrami et al., Begum et al., 2005; Burrai et al., 2014; Cavalcanti et al., 2003; Chou et al., 2005; Hsu et al., 2009; Jedras et al., 2005; Kilic Akca & Tasci, 2016; Yan et al., 2015). The only cross-sectional study (Ristic-Medic et al., 2014) met all the JBI criteria.

Two case studies were included (Szepietowski et al., 2005; Weishaar, et al., 2003). No follow-up studies were conducted. One did not clearly report the site nor demographic information (Weishaar et al., 2003).

Of the seven quasi-experimental studies, six met the JBI criteria (Kilic Akca et al., 2013; Cürcani & Tan, 2014; Lin et al., 2011; Okada & Matsumoto, 2004; Ro et al., 2002; Zare et al., 2018). One (Gao et al., 2002) did not have a control group and appropriate statistical analysis was unclear.

Results

The data in the reviewed literature was separated into the following treatment interventions – acupressure, acupuncture, aromatherapy, homeopathy, music therapy, oral supplements, thermal therapy and topical application. Each of these interventions are summarised below.

Acupressure

The effect of acupressure on pruritus was studied in four trials, with a total of 275 participants and all forms of intervention showing statistically significant efficacy (Jedras et al., 2003; Kilic Akca et al., 2013; Yan et al., 2015; Kilic Akca & Tasci, 2016). While the participant numbers across the studies were small, the studies consistently found similar benefits, allowing for a high level of generalisability. Methods of acupressure varied, including traditional Mongolian methods, auricular acupressure and acupoint stimulation.

Acupuncture

Acupuncture was studied in a RCT (Chou et al., 2005) and one quasi-experimental trial (Gao et al., 2002) (n=74). A statistically significant benefit was reported in both studies.

Aromatherapy

Two quasi-experimental studies with a pre-test / post-test design investigated the effect of aromatherapy on haemodialysis patients (n=163). Both studies (Cürcani & Tan, 2014; Ro et al., 2002) used essential oils and a similar application technique and demonstrated a significant benefit in the group undergoing the intervention.

Homeopathy

One double blind RCT (n=20) was reported using a homeopathy treatment referred to as Verum medication vs placebo (Cavalcanti et al., 2003). The Verum did not reach a

statistically significant benefit compared to the control group at the end of treatment.

Music therapy

Burrai et al. (2014) reports the effects of live saxophone music on participants undergoing haemodialysis (n=114). Physiological parameters such as blood pressure and oxygen saturation in addition to pain, mood and itch were measured via pre-test / post-test design, and compared with a control group. Participants were randomised. A statistically significant reduction in the itching level of the music group was measured compared to the control group.

Oral supplements

A variety of oral supplementation were studied including turmeric, herbs and dietary fatty acids. Pakfetrat et al. (2014) analysed the effects of turmeric in a double blind placebo-controlled RCT (n=100) over 8 weeks. Biochemical markers along with pruritus scores were measured pre-test / post-test, with a significant reduction in mean pruritus scores. The effect of the herb *Fumaria parviflora* L (FP) was studied in a double blind placebo-controlled RCT (n=63) by Akrami et al. (2016). A statistically significant benefit occurred in the first 4 weeks. A further 4 weeks after discontinuation of the herb indicated an ongoing benefit. A double-blind RCT of supplementation with N-3 and N-6 polyunsaturated fatty acids (fish oil and safflower oil) indicated no significant benefit to pruritus (n=35) (Begum et al., 2004). The effects of dietary milled seed mixture were measured in a cross-sectional dietary intervention study (n=65) (Ristic-Medic et al., 2014). The study reports an improvement in pruritus scores in participants but no statistical evidence was specifically provided.

Thermal therapy

Two studies on thermal therapy were carried out on patients undergoing haemodialysis (n=81). Hsu et al. (2009) reported in a double-blinded RCT that there was no statistical benefit between the intervention and the control group. Zare et al. (2018) completed a quasi-experimental study between an interventional and control group and showed a statistically significant benefit in treating pruritus with thermal therapy. Frequency of intervention and study design differed between the two studies.

Topical application

There were five studies on a variety of topical applications (n=162). Ointment containing endocannabinoids was found to provide significant efficacy in managing pruritus in participants on haemodialysis (Szepietowski et al., 2005), while Weisshaar et al. (2003) reported no significant benefit with topical capsaicin. Quasi-experimental studies found that baby oil (Lin et al., 2011) and aqueous gel (Okada & Matsumoto, 2004) were beneficial in treating pruritus. A prospective double-blinded RCT on topical gamma-linolenic acid (GLA) also demonstrated efficacy (Chen et al., 2006).

Discussion

There were a wide variety of CAM therapies and differing study designs, making study comparison and outcomes difficult. While RCTs provide the best level of evidence, they are not always practical in the clinical setting. Non-randomisation is often a pragmatic way of dealing with groups within a haemodialysis setting where blinding of participants and those giving the therapy may not always be possible. To manage these confounders, Cürçani and Tan (2014) split the samples into dialysis day cohorts depending on the days of the week that participants attended the dialysis unit.

“Observational studies (cohort and case-control designs) provide initial evidence for interventions which can later be tested in randomised trials” (Harrison et al., 2017, p. 361). This was demonstrated in the RCT by Hsu et al. (2009) which was repeated in a quasi-experimental interventional study (Zare et al., 2018). Interestingly, the observational study on thermal therapy indicated a significant improvement in pruritus which was not found in the RCT on the same intervention. Harrison et al. (2017, p.361) suggests that this can occur because observational studies “cannot prove that an observed relationship is causative”, and that results can be confounded by variables not included in the analysis.

Other study confounders included variation in study size, duration of intervention and follow-up. All studies displayed heterogeneity in design, duration and participant characteristics. This was true for RCTs as well as observational studies. For instance, acupuncture was studied in one RCT and one quasi-experimental study using the same Quichi point (L1/11); however, study design, sample size, number and duration of interventions and period of follow-up varied.

Different study designs on the same CAM also showed the difficulty in removing variables and achieving consistent results for interventions. When the differing studies showed a beneficial outcome, overall confidence in the CAM intervention improved. For example, acupressure was shown to have significant efficacy despite different techniques of application and study designs. Three out of the four reviewed studies were RCTs (Jedras et al., 2003; Kilic Akca & Tasci, 2016; Yan et al., 2015), with the one non-randomised trial (Kilic Akca et al., 2013) providing evidence to support the later RCT by the same author in 2016. Similarly, the two acupuncture studies also showed efficacy of treatment despite different study designs (Chou et al., 2005; Gao et al., 2002).

Unfortunately, none of the therapies were repeated in the oral supplement and topical application groups. Of the four studies on oral supplementation, two out of the three RCTs (Akrami et al., 2016; Pakfetrat et al., 2014) found that FP and turmeric had a statistically significant benefit. Further follow-up studies on these two supplements are required to strengthen the evidence. The cross-sectional study on the effects of oral milled

seed mixture, while focused on the outcome of inflammatory markers, noted reduction in pruritus as an additional benefit (Ristic-Medic et al., 2014). There was only one RCT within the topical application group. This study demonstrated a benefit in the application of GLA and reported one adverse reaction, a rash (Chen et al., 2006). Two studies in this group were quasi-experimental (Lin et al., 2011; Okada & Matsumoto, 2004), reporting a benefit from the application of baby oil and aqueous gel. A case study on topical cannabinoids also demonstrated a benefit (Szepietowski et al., 2004). However, as these are single studies on each intervention, more evidence will be required before health professionals can confidently claim each intervention as safe and efficacious.

Some CAM therapies included highly specialised practices such as acupuncture, acupressure and homeopathy. Whilst not being administered by a medical practitioner, these therapies still require a level of knowledge and skill that most conventional health professionals do not have. This emphasised the importance of advising patients who are choosing CAM therapies to find the best practitioners.

Data capturing methods varied across all studies, with the VAS tool reported as being used the most consistently in nine out of 21 studies (Kilic Akca et al., 2013; Kilic Akca & Tasci, 2016; Yan et al., 2015; Cürçani & Tan, 2014; Akrami et al., 2016; Hsu et al., 2009; Chen et al., 2006; Szepietowski et al., 2004; Okada & Matsumoto, 2004). The duo pruritus scale was also used in a number of studies (Ro et al., 2002; Akrami et al., 2016; Begum et al., 2004), while Zare et al. (2018) cited the Yosipovitch pruritus questionnaire. However, the majority of studies did not specify the pruritus scale/questionnaires used, leading to a decrease in generalisability of results across studies. The use of a consistent validated pruritus scoring method across all studies of the symptom group would be highly beneficial, providing more opportunity for meta-analysis.

A review of the participants' geographic demographics indicate that CAM studies are under-represented in Western countries where English is the first language. The majority of studies originated from non-Western countries, i.e. Iran (3), Turkey (3), Taiwan (3), Korea (1), China (3), Japan (1), six from European countries – Serbia (1), Poland (2), Brazil (1), Germany (1), Italy (1) – and one from the USA (1). It could be argued that non-Western countries have a stronger alternate medicine culture, and are thus more inclined to trial CAM therapies within the conventional medical environment than Western countries. Further study into local cultural beliefs around the use of CAM and their effect on participants' response and healthcare professionals' attitude towards promoting usage is required. It was also noted that the majority of patient population studied was in the haemodialysis group. This is likely because this group regularly attends treatment, making them easier to study.

Conclusion

The only studies claiming consistent statistical significance were for acupressure, acupuncture and aromatherapy. All other interventions demonstrated variable statistical significance. All studies showed limited negative impacts on patients from the use of CAM therapies.

There is a significant gap in the literature regarding the benefits of CAM therapies for treating pruritus in patients with ESKD. To create a stronger body of evidence further pilots and observational studies are needed on specific CAM interventions and, where feasible, RCT design studies should be initiated on the same intervention. This will rule out confounding factors that may affect the results of observational studies.

A broad population of patients with ESKD should also be included in the studies with longer periods of follow-up. As the mechanism of uraemic pruritus is not well understood, a broader cross-section of participants with ESKD would allow researchers to gain valuable insight into both cause and treatment efficacy. This will assist in identifying how long the efficacy of the intervention lasts, the recommended dosage or treatment duration, and any potential long-term adverse health outcomes. It is also recommended there be standardisation of measurement tools for each symptom studied.

CAM is now part of the health and wellbeing subculture within Australia (von Conrady & Bonney, 2017). Patients are self-medicating using CAM so, regardless of possible scepticism by health professionals about the benefits, further research is needed in order to advise on safety and efficacy. It would be wise to encourage further discussion on the use of CAM with ESKD patients, and integrate that knowledge into the health assessment process so that interventions can be safely monitored in each individual.

Limitations

This review was limited to articles available in English and full text. Due to the heterogeneity of the studies, the results were unable to be combined into a formal meta-analysis.

Conflict of interest

The authors declare no conflicts of interest.

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Table 3. Summary of findings

Author (year) / country	Treatment dose and duration	Study design, sample size	Data collection method	Statistical significance between treatments	Limitations / adverse reactions
Acupressure					
Jedras et al. (2003) Poland	Multiple acupressure points (140) administered in a 15–20 minute session by the same practitioner 3 times a week for 15 sessions.	RCT n=60 patients	PS measured at beginning after 6, 12 and 18 weeks via questionnaire.	Yes	PS tool not mentioned as previously validated. Small sample size. No control group. Nil reported adverse effects.
Kilic Akca et al. (2013) Turkey	IG received acupressure applied using a TENS apparatus and the CG received no acupressure. Acupressure occurring three times per week for 6 weeks for a total of 18 treatments.	Non-randomised controlled trial. n=78 patients	VAS and PS pre-test / post-test.	Yes	Non-blinded study. Participants continued to use antihistamines. Participants' personal traits such as diet, treatment adherence and hygiene have impacted results.
Kilic Akca & Tasci (2016) Turkey	Acupressure and transcutaneous electrical acupoint stimulation (TEAS). Applied x 3 per week during the 4 weeks of the study on 1) the large intestine (LI-1) or 2) acupressure points on the arm, for a total of 12 sessions.	RCT HD Participants were randomly assigned to the following groups acupressure n=25 TEAS n=24 or CG n=25.	VAS collected at baseline and again post treatment.	Yes, results for participants in the acupressure and TEAS groups demonstrated significant effectiveness compared to the control group. No differences were found between the acupressure and TEAS patients.	Short follow-up period. Nil reported adverse effects.
Yan et al. (2015) China	Auricular acupressure x 3 per week for 6 weeks.	RCT IG n=32 patients CC n=30 patients	VAS and biochemical markers were compared before and after the study.	Yes	Small trial sample size. Short duration. Nil reported adverse effects.
Acupuncture					
Chou et al. (2005) Taiwan	Single acupoint (Quichi (LI11) 3 times per week for 1 month with follow-up. Acupuncture was applied for the same duration in the control group but at a non-acupoint.	RCT n=40 patients	Patients responded to a PS pre-intervention at 1 month and again on 3 month follow-up.	Yes	Participants reported soreness at elbow joint.
Gao et al. (2002) China	Acupuncture compared with Western medicine therapies. n=34 acupuncture group (Quichi (L1 1) and Zusanli (ST 36) with thrusting reinforcing method of 30 mins x twice a week for 4 weeks. n=34 drug administration group 4mg chlor-trimeton orally 3 times per day and ointment for dermatitis applied 3 times per day.	Quasi-experimental case study n=68 patients	Pre- and post-treatment method not described.	Statistical significance claimed 22 cases = showed improvement (64.7%) 10 cases = nil effects (29.4%) Total effective rate = 70.6%	Equipment, time, costs, (this was not expanded on in the body of the article) side effects and failure to maintain effects in drug treatment group when medications were withdrawn. Insufficient detail re: data collection, observation methodology and analysis of results. No control group.

Table 3. Summary of findings (continued)

Author (year) / country	Treatment dose and duration	Study design, sample size	Data collection method	Statistical significance between treatments	Limitations / adverse reactions
Aromatherapy					
Cürçüoğlu & İnan (2014) Turkey	Aromatherapy massage three weekly HD sessions for ~7–15 minutes for each region of the pruritus over 6 weeks.	Prospective, pre-test & post-test quasi-experimental design IG n=40 patients GC n=40 patients	VAS and patient questionnaires were completed pre- and post-test	Yes	A non-randomised design lacked an equivalent treatment control group to estimate effectiveness of aromatherapy massage; it is not clear that the positive effects were due to the aromatherapy, the massage or both.
Ro et al. (2002) Korea	Aromatherapy applied as massage 7 mins x 3 times / week for 4 weeks	Quasi-experimental study n=29 patients	Pre-test / post-test modified duo scale.	Yes	Small sample size. Massage not given to control group.
Homeopathy					
Cavalcanti et al. (2003) Brazil	Homeopathic treatment. Dose modified for each participant by homeopathic physician. 60 day follow-up.	Randomised placebo-controlled double blind trial n=20 patients	Data collected over 60 days with four reviews attended each fortnight. Tool not specified.	No	The homeopathic treatment or medication was changed or continued during the intervention according to partial outcomes and the homeopathic physician's judgement.
Music therapy					
Burrai et al. (2014) Italy	Saxophone music. 30 minutes of live saxophone music per week for 4 weeks.	RCT IG n=57 CG n=57	A pre-test / post-test design.	Yes, there were statistically significant differences in the measured in itching, oxygen saturation, pain and mood and itching levels.	No blinding. Limited to one HD ward. Only one renal nurse provided the music, hence it is difficult to determine if improvements in itching were in part due to the relationship between the nurse and the patient.
Oral supplementation					
Akrami et al. (2016) Iran	Oral supplementation of FP (<i>Fumaria paniflora</i>) 1000mg x 3 times per day for 8 weeks.	Randomised, double-blind, placebo controlled trial with two parallel arms n=63 patients	VAS, duo-(pruritus) scores, serum interferon level, interleukin-4 and high sensitivity C-reactive protein were used to determine effectiveness of intervention and measures were collected before and after treatment.	Yes	Small sample size. Short duration. n=1 gastric pain.
Begum et al. (2004) USA	Oral supplementation N-3 and N-6 polyunsaturated fatty acids. 6 capsules/day for 16 weeks.	Prospective, double-blind RCT n=22 patients	Pre-test / post-test subjective pruritus questionnaire adapted from the duo questionnaire. A 3-day food record was obtained prior to supplementation.	No	A small sample size. Short duration. No food records obtained post-trial to ascertain if participants had modified diet during study period.
Pakfetrat et al. (2014) Iran	Oral supplementation of turmeric 500mg x 3 times per day for 8 weeks.	Parallel double-blinded randomised placebo-controlled trial n=100 patients	Pre-test / post-test design was used to compare PS and biochemical markers in each group. Spearman's correlation used.	Yes	Small trial sample size. Short duration.

Table 3. Summary of findings (continued)

Author (year) / country	Treatment dose and duration	Study design, sample size	Data collection method	Statistical significance between treatments	Limitations / adverse reactions
Ristic-Medic et al. (2014) Serbia	Oral supplementation of milled sesame/pumpkin/flax seed mixture 30g/day in 200mls fat free milk for 12 weeks.	Analytical cross-sectional study n=65 patients	Pruritus questionnaire and biochemical markers.	No, seed mixture reported to improve the symptoms of pruritus in all patients; however, no statistics provided to support this.	No control group. Study focus was on inflammatory markers.
Thermal therapy					
Hsu et al. (2009) China	Targeted thermal therapy at Sanyinjiao acupoint. Far-infrared rays at 40°C for 15 mins x twice weekly for 18 treatments – 9 weeks.	Double blind RCT n=21 patients Control: plain adhesive patch on Sanyinjiao acupoint	VAS and PS measured at pre-, mid- and post-test. Biochemical markers tested pre and post.	No	Possible placebo effect in control group due to the plain adhesive patch on the acupoint. Small sample size and short study duration. Possible ineffective acupoint. Nil reported adverse effects.
Zare et al. (2018) Iran	Thermal therapy: far-infrared (FIR) radiation at 40°C for 15 minutes daily in 18 sessions.	Quasi-experimental study n=20 patients It is not stated, but assumed all participants completed the study	The intervention was evaluated in three intervals: pre-intervention, 1 month later (mid-test), and post-intervention (after 2 months), using the Yosipovitch pruritus questionnaire.	Yes	Variation in treatment time due to interruptions. Small sample group. All male participants. Short duration.
Topical application					
Chen et al. (2006) Taiwan	Topical GLA: 2 weeks daily application followed by 2 weeks washout and crossover.	Single-centre prospective, RCT placebo-controlled crossover study n=17 patients	VAS and PS, laboratory assays before and after each treatment period.	Yes	Adverse drug reaction. GLA dose was titrated from 30mg/day as tolerated by participants.
Lin et al. (2011) Taiwan	Unchilled/chilled baby oil 15 minutes once daily for 3 weeks.	Quasi-experimental design study. n=93 patients	Pre-test / post-test itch severity scale.	Yes, reduction in pruritus. No difference between chilled and unchilled oil.	Rash
Szepietowski et al. (2004) Poland	Topical cannabinoids applied twice daily for 3 weeks and follow-up 14 days post discontinuation of treatment.	Case study n=21 patients	Pruritus was evaluated by the same investigators using 2 pruritus scoring methods: VAS and questionnaire. Baseline, day 7, 14, 21, and follow-up.	Pruritus completely eliminated in 38.1% of patients 52.4% patients' results satisfactory 9.5% therapeutic result poor	
Okada & Matsumoto (2004) Japan	Aqueous gel applied twice daily for 2 weeks. 4 week follow-up period.	Quasi-experimental design IG n=20 patients CC n=20 patients	VAS and skin dryness pre, mid and post.	Yes, VAS score for itching significantly decreased in the treatment group at 2 weeks.	
Weishaar et al. (2003) Germany	Intervention – capsaicin 0.05% liniment on the upper back x 3 times daily for 5 days.	Experimental case controlled study with parallel arm IG n=11 patients CG n=10 healthy volunteers	Study parameters investigated were: wheal + flare reactions, itch + alloknesis after serotonin + histamine iontophoresis in treated and untreated skin.	No	Very small scale study. Short study duration. Test subjects applied the treatment themselves. Local burning and stinging.

Legend: CG = control group, DCS = detailed cumulative score, GLA = gamma-linolenic acid, HD = haemodialysis, IG = intervention group, PS = pruritus score, VAS = Visual analogue scale

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