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Review Article

The effectiveness of complementary and alternative medicine therapy in reducing pain in diabetic neuropathy: A systematic review

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Abstract

Background: Pain is quite often felt in approximately 30 to 50% of people with diabetic neuropathy. As a result, the quality of life is low, indicated by the high morbidity and mortality rates. The availability of symptomatic pharmacological agents has the potential to have side effects and adverse effects in the elderly and in addition to the high risk of addiction. Complementary therapy and alternative medicine in chronic pain are clinically safe, cost-effective, and affordable. However, scientific evidence of its effectiveness is limited.
Objective: This systematic review aims to evaluate the intervention modalities and the effectiveness of complementary and alternative medicine therapy in diabetic neuropathy pain.
Methods: The searched literature databases included PubMed, ProQuest, ScienceDirect, EBSCO host, DOAJ, Clinical Key for Nursing, and Cochrane. The criteria for the article, among others, focus on complementary therapy and alternative medicine in diabetic neuropathy pain, publications in the last five years, full text, and in English.
Results: Fifteen articles were identified in reporting the effectiveness of complementary therapy and alternative medicine in reducing diabetic neuropathy pain, including mindfulness-based stress reduction, mindfulness meditation, relaxation, whole-body vibration, Abzan, aerobic resistance training, nano curcumin, Citrullus colocynthis, dietary, acupuncture, laser, and reflexology.
Conclusion: Most scientific evidence reports the effectiveness of complementary and alternative medicine therapies in reducing pain in diabetic neuropathy, thus strengthening its application as an adjunct to conventional medicine is needed.

Keywords: complementary and alternative medicine; neuropathy diabetic; pain

Background

Diabetic neuropathy (DN) is nerve damage due to metabolic disorders associated with Diabetes Mellitus (DM) (Lewis, Dirksen, Heitkemper, & Bucher, 2014), 30-50% accompanied by pain which adversely affects QoL (Aslam, Singh, & Rajbhandari, 2014), morbidity, and mortality with a large number (Iqbal et al., 2018). Pain management remains a crucial aspect of symptom treatment for DN (Iqbal et al., 2018). Proper DN pain intervention is essential.

Both pharmacological and nonpharmacological can treat pain. Pregabalin, Duloxetine, and Gabapentin are recommended as pharmacological treatments for DN pain (American Diabetes Association, 2020), but there is therapeutic intolerance (Spallone, Lacerenza, Rossi, Sicuteri, & Marchettini, 2012), high risk of addiction and side effects may be more severe in elderly (American Diabetes Association, 2020). The best combination therapy for DN pain management is needed (Peltier, Goutman, & Callaghan, 2014). In DN treatment, pain professionals have begun to combine complementary and alternative medicine (CAM) with conventional therapy (Lee & Raja, 2011). This is done in order for DN patients to receive additional therapy to reduce DN pain.

The survey results reported 38% at 18 years of age and over and 12% among children in the United States (Cherry & Jacob, 2016), 25.9% in Europe (Kemppainen, Kemppainen, Reippainen, Salmenniemi, & Vuolanto, 2018), 63.1% in Australia (Steel et al., 2018) and Southeast Asia, the highest was in Malaysia (55.6%) using CAM (Peltzer & Pengpid, 2015). CAM has fascinated global healthcare practitioners, patients on the grounds of its ease of application, effectiveness, economic aspects, and specific treatment (Mehta, Dhapte, Kadam, & Dhapte, 2017). This suggests that CAM therapy is part of contemporary health management practice.

Various CAM therapy studies have been carried out on chronic pain, especially acupuncture, massage, and mind-body therapy (Bašić-Kes et al., 2011). Herbal medicines are an alternative to relieving neuropathic pain (Forouzanfar & Hosseinzadeh, 2018). Acupuncture/acupressure, tai chi/qi gong, hypnosis, meditation, music therapy, yoga, massage, reflexology, and reiki improve breast cancer pain relief (Behzadmehr, Dastyar, Moghadam, Abavisani, & Moradi, 2020). Based on this evidence, CAM therapy can be used in comprehensive pain management.

Several types of CAM therapy have advantages, including clinically safe and cost-effective acupuncture (Bašić-Kes et al., 2011), low-risk massage, and mind-body as one of the safest integrative therapies, especially for the elderly group (Bauer, Tilburt, Sood, Li, & Wang, 2016). Despite significant advances in therapy, symptomatic treatment for DN pain is less than optimal (Aslam et al., 2014). Further studies are needed for more effective treatment of DN pain (Tesfaye et al., 2011). RCTs and statistically significant results are required (Lee & Raja, 2011). But there is a gap in understanding the effectiveness of CAM therapy on DN pain. Therefore, this review aims to systematically evaluate the intervention modality and effectiveness of CAM in DN pain.

Methods

Study Design

This Systematic Review study uses the PRISMA checklist-guideline 2009 (Moher, Liberati, Tetzlaff, Altman, & Group, 2014). The inclusion criteria were: CAM intervention in DN pain, randomized controlled trial (RCT) and pilot study RCT, full text, English, and five years. While the exclusion criteria were: CAM therapy with quasi-experimental articles, cross-sectional, case reports, not in English, and outcomes other than pain. The clinical questions are based on PICO (patient, intervention, comparison, and results) (Eriksen & Frandsen, 2018; Polit & Beck, 2009), P: Diabetic Neuropath, I: CAM, C: standard care, placebo, O: Pain. So, the research question is, “is there any effect of giving CAM therapy compared to standard care/placebo on DN pain reduction?”

Search Methods

The literature search included seven databases: PubMed, ProQuest, ScienceDirect, EBSCO host, DOAJ, Clinical Key for Nursing, and Cochrane. Keywords are based on free terms: “Boolean operator AND/OR diabetic neuropathy AND Therapy complementary and alternative medicine AND Standard care OR placebo AND Pain”.

Assessment of Article Quality and Risk of Bias

The article eligibility was assessed using the Critical Appraisal Skill Program (CASP) RCT (CASP, 2013), and the risk of bias was evaluated using the Cochrane Risk of Bias Tool: + (Low risk of bias), - (High risk of bias), ± (Unclear risk of bias) (J. P. T. Higgins et al., 2011)

Data Extraction, Management, and Analysis

The extraction of the information included: researcher, year, country, CAM category, method, objective, participant, intervention, and study outcome. The results of the research articles were

assessed with a mean difference, confidence interval (*CI*), and *p*-value, reported in a narrative, qualitative manner by the author and two co-authors.

Ethical Consideration

Ethical Clearance was obtained from the Ethics Committee of the Hasanuddin University Faculty of Medicine with Ethical approval Recommendation Number: 794 / UN4.6.4.5.31 / PP36 / 2020.

Results

Study Selection

Screening on seven databases identified 452 articles with human subjects. 33 duplicated articles, 398 irrelevant to the research question, three articles that were not full text, and three articles that were not English were excluded. Finally, only 15 articles met our review criteria (Figure 1).

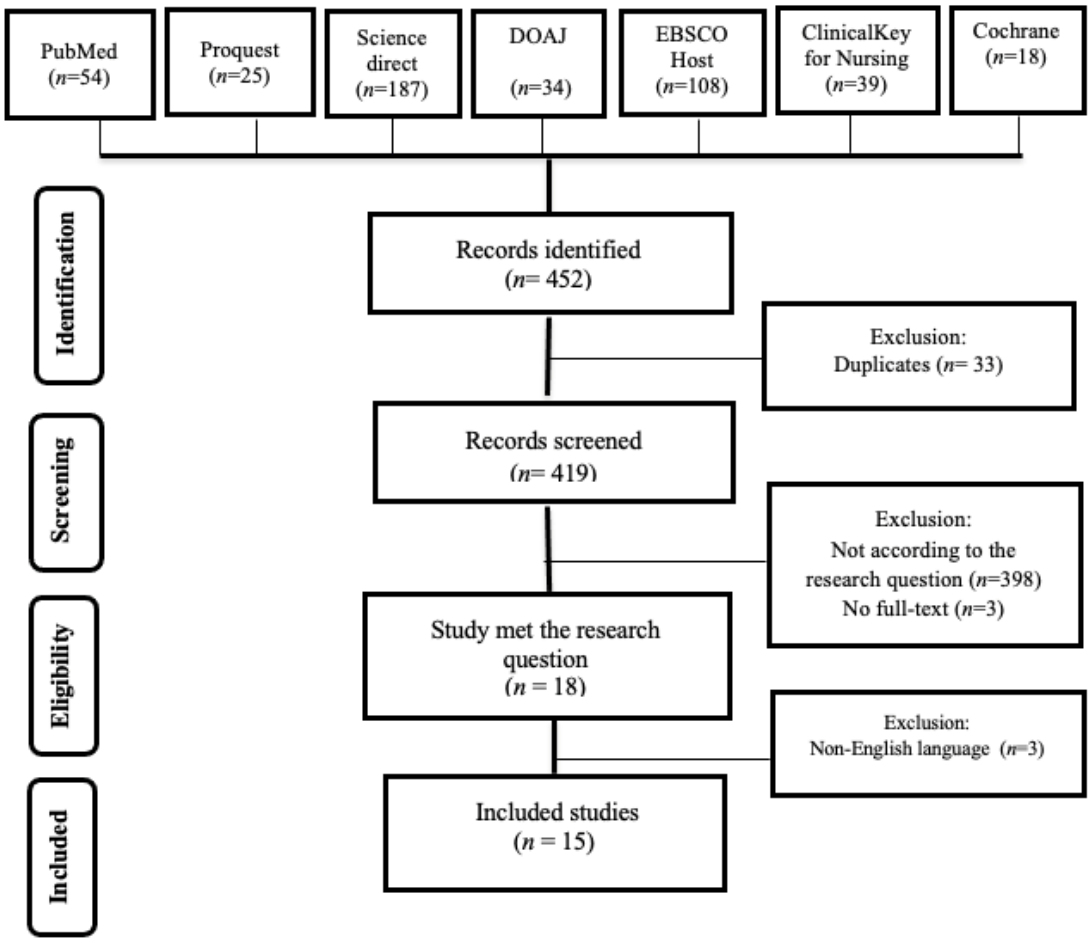

Figure 1 Flowchart of the study selection and inclusion process

Collected Study

These 13 RCT and 2 Pilot study RCT articles describe the effectiveness of CAM therapy in DN pain. Overall, the subjects used (*n* = 843) were distributed as follows, four studies from Iran, three studies from the United States, two studies from India, and one each from Canada, Pakistan, Turkey, Myanmar, KSA, and Egypt (Table 1).

Assessment of Study Feasibility

Fifteen studies were declared eligible and approved by the authors and two co-authors. However, two studies are not applicable using CASP (Shanb et al., 2020; Win, Fukai, Nyunt, & Linn, 2020).

Risk Bias on the Study

In the assessment of the risk of bias, it was found that the majority were with a moderate risk of bias (9

studies), a low risk of bias (5 studies), and a high risk of bias (1 study).

Characteristics of the CAM Intervention Sample on DN Pain

Most studies reported patients with DN pain, type 2 DM, VAS pain score of 4.83, pain duration of 6 to 12 years (Asadi et al., 2019). Most samples were 105 (Hussain & Said, 2019), with an average age of 59 years and 544 (64%) with the female gender.

Application Technique and Duration of CAM in DN Pain

A total of five studies provided 12 weeks of intervention, namely Mindfulness Meditation (Hussain & Said, 2019), hand and foot exercise (Win et al., 2020), acupuncture with 10-15 minute needle placement, and 20-40 minute needle retention (Chao et al., 2019). Progressive muscle relaxation at home 20 minutes via audio recording (Izgu et al., 2020) and deep tissue laser therapy (DTLT) 2 times a week (Chatterjee et al., 2019).

Five studies demonstrated the shortest duration of the intervention, the vibrating platform-style Whole Body Vibration (WBV) therapy, for four weeks (Kessler, Lockard, & Fischer, 2020). Undergoing therapy in warm water for four weeks every night before going to bed, both feet are soaked in a bath of 5 liters of warm water (Vakilinia et al., 2020). Undergo WBV therapy for six weeks consisting of warm-up, WBV, and cycling gradually over 5–10 minutes (Jamal et al., 2019). Two studies with an intervention duration of 8 weeks were undergoing mindfulness-based stress reduction (MBSR) workshops for eight weeks, 2.5 hours per session (Nathan et al., 2017), and undergoing 80 mg of curcumin nano therapy for eight weeks (Asadi et al., 2019). Four studies demonstrated the longest duration of the intervention: undergoing a combination of resistance-aerobic training for 16 consecutive weeks (Parsa, Hosseini, Bije, & Nia, 2018), following a low-fat plant-based diet for 20 weeks (Bunner et al., 2015); and undergoing 2 mL topical Citrullus colocynthis therapy for 36 weeks (Heydari, Homayouni, Hashempur, & Shams, 2016). Magnetic therapy was administered for 20 minutes/session for 36 weeks (Shanb et al., 2020) and underwent foot reflexology therapy 30 minutes/day for 48 weeks (Ibrahim & Rizk, 2018).

Pain Instruments in CAM Intervention

Six studies used the Visual Analog Scale (VAS) (Chatterjee et al., 2019; Izgu et al., 2020; Kessler et al., 2020; Parsa et al., 2018; Shanb et al., 2020; Win et al., 2020)**,** two studies used the Neuropathic pain scale (NPS) (Chatterjee et al., 2019; Heydari et al., 2016). Two studies used the numeric rating scale (NRS) (Chao et al., 2019; Heydari et al., 2016)**,** Two studies used The McGill Main Questionnaire (Bunner et al., 2015; Vakilinia et al., 2020)**,** two studies used the Brief Pain Inventory (BPI) (Nathan et al., 2017) and the BPI modified painful diabetic peripheral neuropathy (BPI-DPN Q4) (Hussain & Said, 2019)**,** Two studies used the Needs Assessment of Neuropathic Symptoms Pain Scale (LANSS) (Ibrahim & Rizk, 2018; Jamal et al., 2019)

Effects of CAM on DN Pain

Based on the 13 out of 15 studies revealed that CAM therapy could reduce DN pain with 11 types of CAM therapy, namely pain severity decreased after administration of MBSR from baseline -1.92(-3.74 to -1.10) (p<0.001) (Nathan et al., 2017)**,** DN pain decreased after giving Mindfulness Meditation 2.2 +0.1 (95% CI -2.50 to -1.80) (p<0.01) (Hussain & Said, 2019)**,** pain severity was lower after administration of Relaxation VAS 4.0 (p<0.05) (Izgu et al., 2020)**,** pain level decreased after administration of Abzan (- 12,984), (95% CI -25,148 to -0.819) (p=0.034) (Vakilinia et al., 2020).

Decreased pain level after Aerobic Resistance Training (2.25 ± 3), (p= 0.01) (Parsa et al., 2018)**,** leg pain symptoms decreased after administration of Nano Curcumin (p= 0.01) (Asadi et al., 2019)**,** pain reduction was greater after administration of Citrullus Colocynthis (3.89) (95% CI 3.19 to 4.60) (p <0.001) (Heydari et al., 2016)**,** change in pain after taking Dietary- 9.1 points (11.4) -8.2 (95% CI -16.1 to -0.3) (p= 0.04) (Bunner et al., 2015), change in pain intensity was lower after acupuncture-2.06 points (95% CI -3.01 to -1.10) (p<0.001) (Chao et al., 2019)**,** decreased pain score after DTLT administration, QVAS -54% mean (31.82) SD (19.60) (p<0.001), NPS -183%, mean (-0.61) SD (0.72) (p<0.001) (Chatterjee et al., 2019)**,** reduction in pain after reflexology administration (9.04 ± 8.11) (p<0.001) (Ibrahim & Rizk, 2018) and reduction in pain after giving WBV, NPRS 2.92 ± 1.55, (p<0.001), LANSS 10.23 ± 3.7 (p<0.001); (Jamal et al., 2019) VAS1.26 ± 1.4 (p= 0.019) (Kessler et al., 2020)**.**

Table 1 Description of the study CAM therapy for DN pain

Researcher, year; Country	Method	Aim	Participant	Intervention	Pain Instruments	Outcome	Research Result
(Nathan et al., 2017); Canada	RCT	To test the effect based on the community-based MBSR	62 DN pain patients	Nine sessions of workshops and a control group, an MBSR workshop was offered after the research	BPI	Significant reduction in pain severity from baseline to -1.92 (-3.74 to -1.10) (p<0.001)	Positive effect
(Hussain & Said, 2019); Pakistan	RCT	To compare mindfulness meditation and progressive relaxation	105 DN pain patients	The 30-minute intervention, the control group underwent discussion, 15 minutes, 20 minutes sitting quietly and relaxing for 16 sessions	BPI-DPN Q4	Significant reduction in pain 2.2 + 0.1 (95% CI -2.50 to -1.80) (p<0.01)	Positive effect
(Izgu et al., 2020); Turkey	RCT	To test the effects of progressive muscle relaxation	77 patients DN	Progressive muscle relaxation or mindfulness meditation at home 20 minutes via audio recording. Control group 30 minutes attention control, education, general DM information with booklet.	VAS	Pain severity was significantly lower by 4.0 (p<0.05)	Positive effect
(Win et al., 2020); Myanmar	RCT	To find out the effect of simple hand, finger, and foot exercises	104 DN patients	Receive regular care, DM foot care education, and 10-minute home-based exercise	BRS and VAS	There was no significant difference in pain reduction15.13 (26.48) (95% CI 5.96 to 24.29) (p >0.05)	No positive effect
(Vakilinia et al., 2020); Iran	RCT	To see the effect of Azan to relieve DN pain	60 DN pain patients .	Soak feet every night before bed without massage. Saltwater bath group: warm water + 250 grams of salt Control: received no intervention.	The McGill Pain	Significant reduction in pain level (-12,984), (95% CI -25,148 to -0,819) (p=0.034)	Positive effect
(Parsa et al., 2018); Iran	RCT	To investigate the effects of resistance-aerobic training	24 patients DN	Attend combined resistance-aerobic training three sessions a week	VAS	Significant reduction in pain level (2.25 ± 3), (p=0.01)	Positive effect
(Asadi et al., 2019); Iran	RCT	To know the influence Nano curcumin supplementation	80 polyneuropathic DM patients	Receives 80 mg of nano-curcumin. The control group received 80 mg polysorbate placebo capsules.	TCNS	Significant reduction in leg pain symptoms (p=0.01)	Positive effect
(Heydari et al., 2016); Iran	RCT	To test safety and efficacy of the topical formulation Citrullus colocynthis	40 patients DN pain	2 mL topical C. colocynthis. Sesame oil control group. given twice a day to the plantar and instep surfaces of the feet	NPS and NRS	The reduction in pain was greater (3.89) (95% CI 3.19 to 4.60) (p<0.001)	Positive effect
(Bunner et al., 2015); United States	RCT Pilot study	To evaluate a plant-based diet	34 DN pain patients	Follow a low-fat, plant-based diet. The control group took vitamin B12 supplements (1000 mcg)	McGill Pain Questionnaire and VAS	Significant change in pain -8.2 points (95% CI - 16.1 to - 0.3) (p=0.04).	Positive effect

Table 1 (Cont.)

(Chao et al., 2019); United States	RCT	To check the eligibility, acceptance, and effects of acupuncture	40 patients with DN	Acupuncture 2 times a week. Duration of one hour for diagnostic administration by the acupuncturist. Duration of follow-up assessment and needle placement: 10-15 minutes, and needle retention: 20-40 minutes. The control group received usual care and primary care / DM	NRS	Significant change in pain intensity -2.06 points (95% CI -3.01 to -1.10) (p<0.001)	Positive effect
(Chatterjee et al., 2019); India	Pilot study RCT	To assess the safety and efficacy of DTLT	40 DPN pain patients	Standard care treatment and received DTLT or SLT 2 times a week for four weeks	QVAS and NPS	Significant reduction in pain score QVAS (-54%) (31.82) (19.60),NPS (-183%), (- 0.61) (0.72) (p<0.001)	Positive effect
(Shanb et al., 2020); KSA	RCT	To investigate the effects of adding magnetic therapy	71 DN patients	Magnetic group: magnetic therapy 20 minutes/session, two sessions/week, Laser group: laser therapy 30 minutes Control: receiving DM drugs and analgesics	VAS	Not significant for the reduction in pain -0.01 95% CI (0.29 to -0.31) (p=0.951)	No positive effect
(Ibrahim & Rizk, 2018); Egypt	RCT	To serve therapeutic the efficacy of foot reflexology	100 pain patients DN	Reflexology therapy + foot care guidelines + conventional therapy, control group (foot self-care guidelines + conventional therapy)	LANSS	The decrease was very significant (9.04 ± 8.11) (p<0.001)	No positive effect
(Jamal et al., 2019); India	RCT	This is to determine the effectiveness of WBV therapy	26 DN pain patients	At six weeks of WBV therapy, the control group was given standard medical care, dietary advice, and lifestyle modification.	NPRS and LANSS	Significant decrease NPRS2.92 ± 1.55, LANSS 10.23 ± 3.7 (p<0.001)	Positive effect
(Kessler et al., 2020); United States	RCT	To evaluate efficacy of WBV	20 DN pain patients	Three sessions of WBV therapy per week, 12 minutes/session (4 administrations in 3 minutes, control group with sham vibrations	VAS	Decrease significantly 1.26 ± 1.4 (p=0.019)	Positive effect

Discussion

Design, Feasibility, and Bias Risk of the Study

The effectiveness of CAM for reducing DN pain has been identified and evaluated in this systematic review. All studies used an RCT design, with the majority of CAM therapies having a positive effect on DN pain reduction. RCT is the best type of study to determine causal between intervention and effect (Kabisch, Ruckes, Seibert-Grafe, & Blettner, 2011). In this review, the majority of studies were of moderate risk of bias. The unique strengths of randomization, allocating intervention and blinding to prevent bias (J. P. Higgins et al., 2016). However, one study of low-quality show concern for its applicability in clinical implications.

Sample on the Study

Most of the samples had type 2 diabetes, women, pain duration up to 12 years, and a mean age of 59. This is consistent with the previous theory that DN is more common in older adults (> 50 years) because of the time it takes for nerve damage and pain to occur (Zakin, Abrams, & Simpson, 2019), with an

increased risk for type 2 DM patients, women, the prevalence of DN increases, and 23.5% after seven years (Iqbal et al., 2018). This suggests the need for early fuses, DN pain symptoms, especially in type 2 DM, to prevent the risk of complications.

Duration of Intervention and Pain Instruments in CAM Application

In this review, most of the studies performed CAM over 12 weeks and for pain instruments using VAS, NPS, NRS, McGill Pain Questionnaire, and LANSS. VAS, SF-MPQ are non-specific pain measurements (Nash, Armour, & Penkala, 2019). NPS and Neuropathic Pain Questionnaire (NPQ) measure the quality and intensity of DN pain (Bašić-Kes et al., 2011). Meanwhile, NRS, LANNS, and McGill Pain Questionnaire are validated, best and oldest measurements of neuropathic pain in a numerical rating scale (Tesfaye et al., 2011). This shows the importance of using proper pain measurement instruments in order to get accurate results.

Effects of CAM interventions on DN pain

The identification and evaluation of CAM interventions show significance in reducing DN pain, including MBSR, meditation, relaxation, WBV, Abzan, aerobic resistance training, and nano curcumin, Citrullus colocynthis, dietary, acupuncture, laser, and reflexology. According to previous studies, CAM intervention in the form of acupuncture and mind-body therapy showed its efficacy for chronic pain (Bauer et al., 2016), reflexology is an alternative non-pharmacological therapy in improving symptoms of peripheral DN (Çakici, Fakkel, Van Neck, Verhagen, & Coert, 2016). The more common plants for the treatment of neuropathic pain include Citrullus colocynthis (Forouzanfar & Hosseinzadeh, 2018). It can be concluded that CAM therapy can be said to be effective in reducing DN pain.

Seven other types of CAM interventions also have the effect of reducing DN pain, such as WBV, Abzan, exercise, relaxation, dietary, nano curcumin, and laser. WBV transfers energy with the benefit of glucose regulation (Baute, Zelnik, Curtis, & Sadeghifar, 2019). The relaxation response increases the brain's response to endorphins (Hassed, 2013). Consumption of a low-fat vegan diet can improve glucose tolerance and insulin sensitivity (Barnard, Scialli, Turner-McGrievy, Lanou, & Glass, 2005), and movement, especially aerobic exercise, has the ability to reduce distraction and pain perception (Baute et al., 2019). However, the most effective intervention in this review is Mindbody spirit meditation therapies, which reduce pain early on and have no side effects. Mind-body, one of the safest integrative therapies (Bauer et al., 2016), can be used in the management of chronic pain, sometimes as a single treatment but more commonly as an adjunct (Hassed, 2013). Ultimately, it can be given as an adjunct or alternative therapy for DN pain.

CAM Intervention Side Effects

Most studies reveal no side effects of CAM. As for the side effects that may occur, it is tolerable and does not require additional intervention. In accordance with previous studies that acupuncture is safe and clinically cost-effective, there is a risk of skin irritation, but this problem is relatively rare and easy to treat (Bašić-Kes et al., 2011). Diet modification, exercise, and lifestyle optimization with minimal side effects (Baute et al., 2019). Although most studies reveal the effect of CAM on reducing DN pain, the quality of the studies is moderate.

Strength and Limitation of the Study

To our knowledge, this is the first systematic review to evaluate the effectiveness of CAM therapy to reduce DN pain. In addition, we assessed the side effects of CAM in order to identify clinically safe interventions to generalize. Although the evaluation results of most CAM interventions have the effect of reducing DN pain, there are several limitations, such as the limited sample due to dropouts, no follow-up to confirm the effect of the intervention, the use of different pain measurement instruments. For this reason, a meta-analysis could not be done.

Conclusion

CAM therapy is effective at reducing DN pain and can be used as an adjunct to conventional treatments. However, further studies are needed with good study quality, large sample, the follow-up to further confirm the effectiveness of CAM interventions in reducing DN pain.

Declaration of Conflicting Interest

The authors declare no conflict of interest.

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Author Contribution

Designed and implemented the research (SS and SY), analyzed of the results (SS, SY, and YS), written the manuscript (SS), critically reviewed (SY) and revised the manuscript (SS). All authors agreed with the final version of the manuscript.

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