Review article

Efficacy of herbal medicine for patients with diabetic neuropathies: An updated literature review

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ABSTRACT

Traditional medicine is efficacious to protect complications of diabetes mellitus, such as diabetic neuropathy. Therapy with herbal medicine has been developed for people with diabetes empirically over the years. This literature review aims to assess effect of herbal medicine for patients with diabetic neuropathies. We conducted a literature analysis using articles that were randomized controlled clinical trials (RCTs). Three databases were searched from PubMed, EMBASE, CENTRAL that have been published from January 2000 until October 2021until October 2021 and obtained four articles that met the study criteria. The review analysis results showed a significant effect between Gua Sha therapy, green tea extract, and topical *Citrullus colocynthis* on reducing diabetic neuropathy pain ($p < 0.05$). Nutmeg Extracts did not show significant results on diabetes mellitus pain after being treated for four weeks ($p = 0.063$). The review results in the physical and neural function also showed the significant increase in mean scores. Despite the positive findings, it is too early to conclude on the efficacy of herbal medicine to treat diabetic neuropathy due to the high clinical heterogeneity and the number of sample size of the study was too small. However, it may be indicative of the effect of herbal medicine in reducing pain in diabetic neuropathy.

Keywords: Herbal medicine; diabetic neuropathy; patients.

INTRODUCTION

Diabetes mellitus is a chronic disease and has become a universal concern due to its high morbidity and mortality (1). According to WHO, more than 422 million people have diabetes, most sufferers live in low and middle-income countries. WHO also reported of 5% increase in death of diabetes mellitus between 2000 and 2016. In 2019, 1.5 million deaths were estimated caused by diabetes (2). Diabetes can cause macrovascular and microvascular complications. Coronary heart disease and peripheral vascular disease are macrovascular complications, while microvascular complications include retinopathy, nephropathy, and neuropathy (3).

Diabetic neuropathy (DN) is the most common chronic complication characterized by pain mainly due to the lesions on the somatosensory nervous system and neuropathy or polyneuropathy become the most common type, which results in significant disability and morbidity (4-6). Previous epidemiological studies have reported the prevalence of diabetic neuropathy worldwide at 66%, where the prevalence of diabetic peripheral neuropathy diabetes mellitus (DM) type 2 is 50.8% and type 1 DM is 25.6% (7). Annalisa reports that 14.1% of patients with diabetes have diabetic neuropathy in the United Kingdom and 23.1% in Italy. In the US, people with diabetes age 40 or older are diagnosed with diabetic peripheral neurology about 1-3% (8). Diabetic neuropathy develops gradually over many years resulting in physical and mental consequences affecting a patient's quality of life (9). Diabetic peripheral neuropathy is also reported as a significant cause of decreasing patient's life quality sensory loss, fall-related injuries, leg ulceration, gait instability, and amputation (5,7). Several metabolic and immunological pathways are involved as the pathogenesis of diabetic neuropathy (9). Oxidative stress, inflammation, glycation, ischemia, and aldose reductase hyperactivity are the central mechanisms in neuronal damage, which hyperactive aldose reductase also causes oxidative stress and upregulation of several other pathogenic pathways (10, 11). Therefore, hyperglycemia plays as the main role in the pathophysiology of this disorder (9). Other conditions such as hypertension, hyperlipidemia, and obesity also increase the risk of developing DN. Currently, DN is considered as the complication of diabetes, with its management primarily involving improving glycemic control, administering pain relief, and ensuring ongoing foot care (3, 6). Several drugs, including gabapentin, duloxetine, and tricyclic antidepressants, are currently used to decrease the discomfort effect on patients but those drugs do not have a significant affect on neuropathy and also have a variety of side effects, such as decreased appetite, suicidal behavior, insomnia, dry mouth, arrhythmias, and heart failure (12-14).

The management of diabetes mellitus with herbal medicine has been developed empirically for many

years in China, Indonesia, India, England, and other countries. Evidence from clinical studies suggests that herbs can reduce symptoms, increasing nerve conduction velocity in people with DN (7). Pharmacological studies show that some herbal medicines can reduce oxidative stress and free radicals, inhibit apoptosis and reduce the sorbitol content in cells, and have many advantages over conventional medical approaches in preventing diabetic complications (8). This study provides a summary of the efficacy of herbal medicine for patients with diabetic neuropathy.

MATERIALS AND METHODS

Survey point

The method used a literature study using the PRISMA checklist guideline 2009 in this research. The authors collected articles through search data sources at PubMed, CENTRAL, and EMBASE. Each article collected was read in-depth, summarized, compared and criticized, commented based on previous research evidence on traditional medicine. All data used is public data. In this study, the authors search for articles or journals based on keywords to make it easier to determine which articles or journals are appropriate to use. The following search terms used individually or combined, including their MESH descriptors: diabetic neuropathy, diabetic neuralgia, herbal medicine, phytotherapy, plant extract, herb or herbs, or herbal.

Criteria of the study

This study will only review randomized controlled studies in humans evaluating the effects of herbal remedies on diabetic neuropathy. DN is a type of nerve disorder that can occur in people with diabetes mellitus. This condition is a severe complication of diabetes mellitus caused by metabolic and microvascular disorders. Symptoms of DN range from numbness, tingling, and pain in the extremities to multiorgan problems. Patients with painful diabetic neuropathy usually present with stabbing, burning, or excruciating pain. Participants included in this study are:

1. All patients that suffer from diabetes mellitus regardless of age and gender. The diagnosis of diabetes mellitus is based on internationally recognized criteria.
2. The patient should exhibit symptoms of symmetrical diabetic neuropathy, such as numbness, tingling, or pain in the extremities.

Participants with neuropathy caused by other conditions, such as infections, autoimmune disorders, cancer, will be excluded. The following interventions were analyzed if data were available: Herbal medicine compare to no treatment, herbal medicine compare to placebo, herbal medicine compare to conventional medicine. The control group had no medication, placebo, or conventional drugs used for glycemic control purposes. All articles will independently review research titles and abstracts to find studies that meet the inclusion criteria. If the article met the inclusion criteria, the evaluation of full text was conducted.

Ethical consideration

The authors have wholly observed ethical issues include plagiarism, informed consent, data fabrication and falsification, double publication or submission, and redundancy).

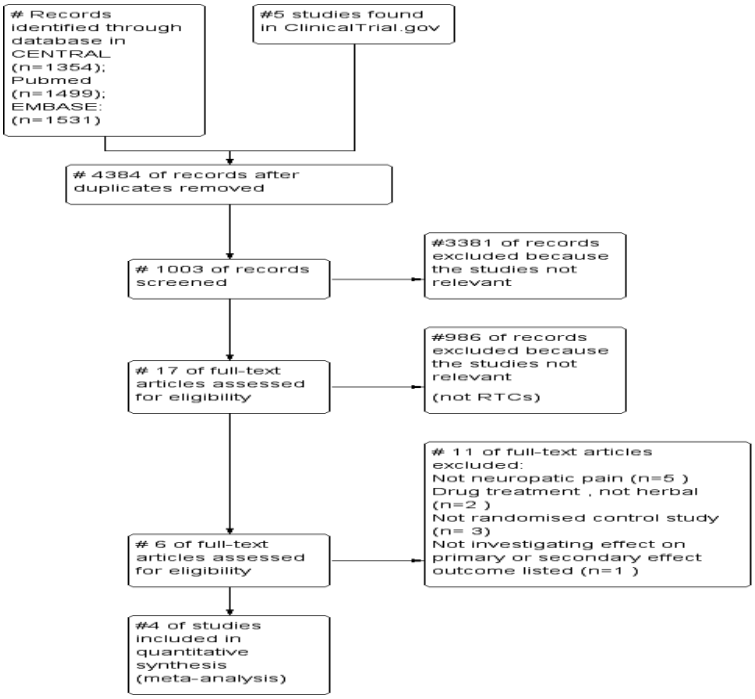

Fig.1: Flow diagram of the study selection process

RESULTS

Characteristics of the trials

The main results of the review articles highlight the impact of herbal medicinal products or preparations on neuropathic pain due to complications of diabetes. Figure 1 shows the number of trials identified. The electronic database and reference search resulted in 4384 publications, of which 4 RTC studies were eligible according to the inclusion criteria set.

Four randomized trials of patients who have diabetic neuropathy were treated with herbal medicine and compared with usual care/placebo. There were gua sha theraphy, green tea extract, nutmeg extract and topical citrullus colocynthis extract that used to treat diabetic neuropathy. The mean age of study participants ranged from 43.3 years to 60.7, with a standard deviation of 15.8 and 11.5. The duration of patients who had diabetes mellitus and had complications of diabetic neuropathy was > 10 years.

There were two research papers with 12 weeks' treatment for patients with DM , one research paper with a treatment of 16 weeks and one with four weeks (Table 1).

Table 1: Summary of the characteristics of the included trials and the assessment of the methodology

First author	Subject (T/C)	Age (T/C)	Disease duration (T/C)	Intervention		Course of treatment (week)
				Treatment	Control	
Xie 2019 (15)	60/59	58.86±11.75 /59.22 ± 9.13	10.10±5.56 / 9.36 ±3.19	Gua Sha therapy	placebo	12 w
Essmat 2021 (16)	96/98	46.7 ± 16.6 / 43.3 ± 15.8	16.4 ± 9.2 / 15.1 ± 5.0	Green tea extract	placebo	16 w
Motilal 2013 (17)	37/37	60.7 ± 11.5 / 59.7 ± 8.1	11.2 ± 8.9 / 11.5 ± 6.6	Nutmeg Extracts	placebo	4 w
Heydari 2016 (18)	28/27	57.36 ± 10.00 / 52.70 ± 10.53	11.57±6.70 / 10.89 ± 6.07	Topical Citrullus colocynthis	placebo	12 w

Table 2: Summary of the effect of herbal medicine on treating diabetic neuropathy

No.	Author and year	Volume	Title	Study design	Result
1.	Xie X. 2019	35	Effect of Gua Sha therapy on patients with diabetic peripheral neuropathy: A randomized controlled trial	Randomized controlled trial	This study used Gua Sha for treating patients with DN. After intervention with Gua Sha for eight weeks and 12 weeks post-intervention, Gua Sha therapy significantly suppressed the severity of neuropathic symptoms, improved sensory function performance, reduced peripheral arterial disease, and controlled plasma glucose better than the control group (all P values < 0.01). They investigated the changes in mean values of TCSS, VPT, ABI, and the level of plasma glucose in the Gua Sha. It showed significant changes from baseline to week 12, suggesting a progressive improvement of Gua Sha therapy in the management of diabetic neuropathy symptoms, sensory function, peripheral arterial disease, and blood glucose levels.
2.	Essmat 2021	43	Green tea extract for mild-to-moderate diabetic peripheral neuropathy A randomized controlled trial	Randomized controlled trial	This study used green tea on treating diabetic peripheral neuropathy. After eight weeks of treatment, patients in the GTE group showed lower VAS scores while TCSS and VPT were significantly lower. As treatment continued, the differences between the groups regarding outcome parameters became clearer at 16 weeks. The results of this study are an indication that GTE intake may have a beneficial value in treating diabetic neuropathy.
3.	Motilal	19	Nutmeg Extracts	Randomized	This study investigated the effect of nutmeg

	2013		for Painful Diabetic Neuropathy: A Randomized, Double-Blind, Controlled Study	controlled trial	extract to reduce pain scores on patients with DN. Significant reductions severely and average pain scores were found in each group ($p \leq 0.001$). The decrease of interference with walking, mood scores and burning, sleep, pins and needles were found in each group ($p<0.05$). Statistically, there were no significant differences in pain reductions between the worst and average pain groups after 4 weeks for any outcome measure.
4	Heydari 2016	8	Topical *Citrullus colocynthis* (bitter apple) extract oil in painful diabetic neuropathy: a double-blind, randomized placebo-controlled clinical trial	Randomized controlled trial	This study aimed to examine the effect of topical *Citrullus colocynthis* extract oil on diabetic neuropathy. The results showed a significant reduction in mean pain score after three months of treatment with *C. colocynthis* (−3.89; 95% confidence interval compared with *C. colocynthis*) while placebo group (−2.28; 95%) ($P < 0.001$). Means changes were significantly higher in the intervention than the placebo group on nerve conduction velocity of the tibial nerve, distal latency of the superficial peroneal nerve and sural nerve, and the sensory amplitude of the sural nerve ($p < 0.001$) In a different domain than WHOQOL-BREF, there was a significant increase only for the mean scores in the physical domain. It may also has an effect on neural function or physical quality of life, which requires further investigation in studies with larger sample sizes and longer duration.

Based on Table 2, all the articles showed the significant effect of herbal medicine to suppress diabetic neuropathy pain except the nutmeg treatment conducted by Motilal *et al.,* (17). In their study, there was no significant difference of treatment groups with placebo after treatment for four weeks. This is an indication that nutmeg extract did not improve diabetic neuropathy pain. This may be because the duration of treatment was only four weeks while other herbal medicines were applied for 12 weeks to 16 weeks, so it was not possible to assess whether any initial response would be sustained in the long term.

DISCUSSION

Diabetic peripheral neuropathy is a common complication of patients with diabetes mellitus that increase morbidity. People with DM, primarily type 2, are mainly over 40 years (19). A study looking at the standardized trend of age from 1990 to 2017 shows that the average age for T2DM prevalence is increasing worldwide, but the slope varies by country, and education, physical activity, and BMI are the most relevant in order of prevalence and trends in each country (20, 21). In this study, the duration of patients who had diabetes mellitus and had complications of diabetic neuropathy was > 10 years. This condition is associated with aging, especially persistent inflammation, which increases susceptibility in people >40 years. It will increase morbidity and also peripheral nerve sensitization. As known that diabetic neuropathic pain affects one-third of adults with diabetes mellitus (22), it is estimated that the prevalence of neuropathic pain among the elderly is higher (23). In chronic diseases, this point is essential to consider not only to investigate the analgesic efficacy and effectiveness of herbal medicinal products for neuropathic pain but also the possible side effects. Previous studies have shown the significance of the treatment results with herbal medicine to treat foot ulcers due to diabetes with a treatment duration of 12 weeks (17). In a previous study, Jinlida Granule, as one of the Traditional Chinese Medicine, was administered in two groups of T2D patients. After 12 weeks, the levels of HbA1c, fasting plasma glucose (FPG), and 2-h postprandial glucose (2-h PG) in the Jinlida Granule group plus metformin were significantly lower than the placebo plus metformin group. Therapy with herbal medicine showed a significant effect for reducing neuropathy pain which included Gua Sha therapy, green tea extract, and topical *Citrullus colocynthis* ($p< 0.05$). However, there is one paper that showed a different result. Nutmeg extracts did not show a significant difference between the treatment group and the control group ($p=0.63$). Rivaz *et al.,* also showed that herbal medicine therapy could lead to several side effects, such as dizziness, drowsiness, mood disorder, and constipation (24). The use of herbal medicine to overcome the problem of diabetic neuropathy still needs to be continued. Based on the research results conducted by Heydari, there are indications of side effects of therapy with nutmeg on nerve function and

physical domains of quality of life that require further investigation in studies with larger sample sizes and longer durations (18). This is a vital thing to study because some herbal medicines known to have a good effect in reducing fatigue have side effects on other organs. All the main findings reported in this review are of limited significance due to the insufficient number of articles to describe the effects of herbal medicine on diabetic neuropathy.

CONCLUSION

Despite the positive findings based on the four high-quality studies, there is evidence regarding the efficacy of herbal medicine to treat diabetes complications, namely diabetic neuropathy. The significant effect of herbal medicine therapy to reduce pain in diabetes complications is also seen from the relative risk. Namely, this reveals the potential role of herbal medicine in the treatment of diabetic neuropathy. More high-quality RCTs are needed to strengthen further the effectiveness and side effects of herbal medicines in treating diabetic neuropathy. The study results also become the basis for further research to see the adverse effects of therapy using herbal medicine for diabetic neuropathic pain because the side effect test of each herbal medicine used has not been well-studied.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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