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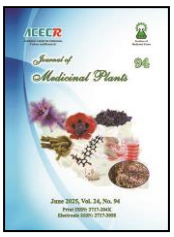

Research Article

The effect of *Achillea millefolium* a widely used plant in Persian Medicine on hemoglobin glycosylate and neuropathy symptoms in type 2 diabetic patients: A randomized clinical trial

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ABSTRACT

Background: Diabetic neuropathy is a prevalent microvascular complication that significantly impairs patients' quality of life. **Objective**: This study examined the therapeutic effect of *Achillea millefolium* oral supplementation on glycated hemoglobin (HbA1C) levels and neuropathic symptoms in individuals suffering from type 2 diabetes. **Method**: In a triple-blind randomized clinical trial, 70 patients with type 2 diabetes attending a diabetes clinic in Rafsanjan were enrolled through convenience sampling and placed into intervention and placebo groups using the minimization technique. The patients in the intervention group received one capsule having 500 mg of aqueous extract of *A. millefolium*. They used the capsules daily for three months. The patients in the placebo group received identically appearing capsules filled with 500 mg of cellulose. Outcomes were assessed with the Michigan Neuropathy Screening Instrument (MNSI) and HbA1C testing, both administered at baseline and after the 3-month intervention period. The data were processed using SPSS-22 software. **Results**: Post-intervention analysis revealed a decrease in HbA1C levels in the *A. millefolium* group in comparison with the placebo group, but no significant intergroup difference was observed (P = 0.17). However, the participants in the intervention group showed a significant improvement in neuropathy symptoms relative to the placebo group (P = 0.001). **Conclusions**: The findings suggest that oral administration of *Achillea millefolium* can effectively alleviate neuropathic symptoms in patients with type 2 diabetes. Nevertheless, further clinical studies need to explore its potential effects on glycemic control.

Abbreviations: HbA_1C, Hemoglobin Glycosylate; MNSI, Michigan Neuropathy Screening Instrument; MS, Multiple Sclerosis

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1. Introduction

Type 2 diabetes is recognized as one of the most prevalent metabolic illnesses globally [1]. In recent decades, the number of individuals diagnosed with diabetes has shown a consistent upward trend, with projections indicating that the global burden may reach approximately 26.6 million and 570.9 million cases by the year 2025 [2]. In Iran, data from 2019 reveal that diabetes was responsible for 20.1% of deaths and accounted for 11.5% of disability-adjusted life years (DALYs) compared to non-communicable diseases [3].

Diabetes may lead to several serious problems and complications, including cardiovascular disease, nephropathy, neuropathy, retinopathy, and a higher mortality rate compared to non-diabetic individuals [4]. Among these, peripheral neuropathy is a common consequence, encompassing a broad spectrum of peripheral nerve disorders with various clinical presentations [5]. Peripheral neuropathies are considered the most prevalent neurological disorders, with an annual incidence rate of 77 per 100,000 people, affecting 1–12% of the general population and up to 30% of older adults [6-8]. The hallmark symptom of diabetic peripheral neuropathy is symmetrical sensory pain, predominantly affecting the lower extremities [9]. Other commonly reported symptoms are abnormal pain sensations, numbness, tingling, and a burning or heated feeling in the affected areas [10]. Several factors are associated with the incidence of peripheral neuropathy, including the duration of diabetes, insulin resistance, central obesity, dyslipidemia, and elevated blood pressure [11]. Nonetheless, evidence indicates that strict glycemic control, particularly through regular HbA1c monitoring, remains the only proven method for preventing or alleviating neuropathic symptoms [12]. Treatment strategies for diabetes and its associated complications range from pharmacological interventions to non-drug therapies [13, 14]. Although several medications exist to manage neuropathic pain, many are accompanied by adverse outcomes [14]. Consequently, there is growing interest in alternative approaches, particularly herbal treatments, for managing diabetic neuropathy [15].

Achillea millefolium, belonging to the Asteraceae family, has been traditionally employed in herbal medicine to address inflammatory conditions, gastrointestinal spasms, liver and biliary disorders, as well as cardiovascular and respiratory ailments [16, 17]. In addition to these uses, it has been adopted in regions such as Mexico and other parts of the world for managing diabetes and its associated complications [18, 19]. The plant contains various bioactive constituents, including monoterpenes, sesquiterpenes, flavonoids, and phenolic acid derivatives, with the antidiabetic properties largely attributed to its flavonoid and phenolic acid content [20–23]. Regarding its therapeutic potential, de Souza et al. demonstrated that administering *A. millefolium* aqueous extract after doxorubicin treatment significantly normalized liver enzyme levels to values observed in the control group [24]. Similarly, Vahid et al. found that *A. millefolium* extract effectively lowered blood glucose, serum lipids, and alkaline phosphatase levels in diabetic mice [25]. Moreover, Karimi et al. observed that the hydroalcoholic extract of *A. millefolium* induced a notable, dose-dependent decrease in blood glucose in streptozotocin-induced diabetic rats [26]. Chávez-Silva et al. further confirmed the antidiabetic potential of *A. millefolium* hydroalcoholic extract, attributing its efficacy to mechanisms such as inhibition of α-glucosidase,

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stimulation of insulin secretion, and potential enhancement of insulin sensitivity [27]. Despite this growing body of evidence, no previous studies have specifically explored the impact of the aqueous extract of *A. millefolium* on blood glucose or diabetes-related neuropathy. Therefore, this study sought to evaluate the impact of oral supplementation with *A. millefolium* aqueous extract on HbA1C levels and neuropathic symptoms in individuals suffering from type 2 diabetes.

2. Materials and methods

2.1. Herbal and placebo capsules preparation

Participants in the intervention group were administered one capsule per day containing 500 mg of *Achillea millefolium* aqueous extract over three months. The capsules were produced by Rafsanjan Essence Daru Co. in partnership with Barich Essence Pharmaceutical Company, Tehran, Iran. In parallel, those in the placebo group received identical capsules filled with 500 mg of cellulose, administered at the same dosage and duration as the intervention group.

Each capsule contained 500 mg of aqueous extract collected from the flowering aerial parts of *A. millefolium*. The plant materials were sourced from the Isfahan Botany Herbarium (specimen no. 9757) and authenticated by Dr. Valiollah Mozaffarian at the Botany Research Division of the Research Institute of Forests and Rangelands in Tehran, Iran. Following collection, the plant specimens were thoroughly cleaned, rinsed, and dried in a cool, dark environment. The flowering branches and leaves were then carefully separated and ground into a fine powder.

The recommended dosage for human consumption ranges between 2-4 grams of dried flowers and stalks [30], which is equivalent to approximately 250-500 mg of dried aqueous extract. For extract preparation, 4 grams of plant material were immersed in the form of powder in 100 ml of distilled water and incubated for 5 to 6 hours at 70 °C—carefully maintained to prevent degradation of active constituents, which occurs at temperatures exceeding 70 °C. The resulting extract was then filtered using filter paper and subsequently dried at temperatures below 40 °C. The final dried extract was encapsulated into 500 mg doses.

2.2. Standardization of the herbal medicine

Quantitative analysis of flavonoid content in the prepared extract revealed luteolin with a concentration of 0.28 mg/g and apigenin with a concentration of 1.58 mg/g. These measurements were conducted by Barich Essence Pharmaceutical Company, Tehran, Iran [31].

2.3. Protocol of study

2.3.1. Patients

This triple-blind randomized clinical trial was conducted in 2022 on individuals with type 2 diabetes visiting the Diabetes Clinic in Rafsanjan in southeastern Iran.

2.3.2. Inclusion and exclusion criteria

The inclusion criteria for enrollment in the study were: diagnosis of type 2 diabetes, age over 40 years, provision of informed consent, no concurrent enrollment in similar research, an MNSI score above 7, a minimum five-year history of diabetes, and absence of hereditary neuropathies or other underlying conditions associated with neuropathy such as chronic uremia. Additional criteria included no history of autoimmune disorders, such as rheumatoid arthritis, MS, or osteoarthritis affecting lower limb joints, no use of anticoagulant medications, no traumatic injuries or fractures resulting in sensory or motor deficits in the lower limbs, no

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known allergies to herbal medicines, no use of tricyclic antidepressants, no regular consumption of medicinal herbs, no active wounds or infections on the legs, no lower limb amputations, and no current pregnancy or lactation. Exclusion criteria included: withdrawal of consent, failure to take the assigned medication or placebo for 8 consecutive days or 6 non-consecutive days within two weeks, relocation, development of illness, emergence of adverse reactions related to the medication or placebo, and death.

2.3.3. Sample size

Based on a previous similar study [28], the sample size was estimated using the mean comparison formula, resulting in an estimated 35 participants per group.

2.3.4. Interventions

The participants were recruited through convenience sampling from among eligible patients meeting the inclusion criteria. Upon obtaining informed consent, the demographic questionnaire and the Michigan Neuropathy Screening Instrument (MNSI) were completed via face-to-face interviews. Additionally, venous blood samples (5 cc) were collected from all participants both before and after the intervention for the measurement of HbA1C levels. Blood samples were placed in coagulation tubes for 40 minutes, and then centrifuged at 1,600 g for 15 minutes. The resulting serum was separated and stored at −70 °C until HbA1C analysis.

The participants were randomly placed into either the intervention or placebo group using the minimization technique. Initially, clusters were formed based on key study variables, specifically HbA1C and MNSI scores. The first four participants were randomly placed into the intervention and placebo groups. Thereafter, each new participant was assigned to the group with the lower cumulative index score to maintain balance across the study variables [29].

The *A. millefolium* aqueous extract and placebo capsules were labeled as A and B and distributed to participants in both groups. Neither the patients nor the researcher were aware of which capsules contained the active extract and which contained the placebo. The data analyst was also blinded to group allocation. After data analysis was completed, the pharmacist disclosed which of the A and B capsules corresponded to the intervention and placebo groups.

2.3.5. Outcomes

The data for this study were collected using the Michigan Neuropathy Screening Instrument (MNSI), a standardized tool with established validity and reliability [32]. The MNSI contains two sections: a 15-item self-administered questionnaire and a clinical test of the lower extremities, which assesses inspection, vibratory sensation, and ankle reflexes. In the present study, only the self-administered questionnaire was utilized. This questionnaire includes 15 yes/no items, where, except for items 7 and 13 (for which a “no” response scores 1 and “yes” scores 0), all other items score 1 for a “yes” response and 0 for “no.” A total score exceeding 7 indicates the presence of neuropathy. Herman et al. used beta values derived from multiple logistic regression analysis to create indicators that predict clinically confirmed neuropathy based solely on this instrument, which demonstrated 99% specificity. The positive and negative predictive coefficients were 84% and 73%, respectively [32]. Furthermore, Fateh et al. validated and confirmed the reliability of the instrument for use within the Iranian population [33].

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The level of HbA1c was measured using a UV2800 UV-VIS spectrophotometer (Mindray Co., China) at the laboratory of Ali-Ibn-Abitaleb Hospital in Rafsanjan. The device was calibrated before measurements, and its reliability was assessed using the test-retest method. Specifically, a blood sample was split into two aliquots, with HbA1c levels measured separately in each. The Pearson correlation coefficient between the two measurements was calculated as 0.86, indicating good reliability. Throughout the study, patients received weekly telephone calls to monitor medication adherence and confirm ongoing eligibility according to inclusion criteria.

2.3.6. Ethical considerations

The study protocol was confirmed by the Ethics Committee of Rafsanjan University of Medical Sciences (IR.RUMS.REC.1401.015) and was registered with the Iranian Registry of Clinical Trials (IRCT20150713023190N13, https://irct.ir/user/trial/63468/view). Informed consent was received from all participants. They were also reassured of the confidentiality of their data and that the study results would be reported anonymously. The participants were also told that their involvement was voluntary and that they could leave the study at any stage without any consequences.

2.3.7. Data analysis

The collected data were summarized using descriptive statistics, such as means and standard deviation. For analytical purposes, independent samples t-test, paired t-test, chi-square test, and Fisher's exact test were employed to compare demographic variables and outcome measures, including the mean scores of HbA1C and neuropathy. All statistical procedures were performed with SPSS software (version 22). P-values smaller than 0.05 were considered statistically significant in all two-tailed tests.

3. Results

The demographic analysis indicated that most of the participants in both the treatment and placebo groups were female, around 50 years of age, married, unemployed, had lower levels of education, and had been living with diabetes for more than five years. The patients in the two groups were not significantly different in terms of these demographic variables as shown in Table 1.

A total of five participants from the intervention group were omitted from the study—three due to lack of cooperation and two due to adverse effects, including nausea and vomiting. Similarly, five patients from the placebo group were excluded—two due to non-cooperation, one due to non-adherence to the medication regimen, and two due to side effects such as headache and nausea. No other complications were reported. To evaluate the safety of the intervention, liver enzyme levels (SGOT and SGPT) were measured post-intervention. The mean SGOT levels were 18.75 ± 6.77 in the intervention group and 17.2 ± 6.51 in the placebo group, while SGPT levels were 24.41 ± 6.84 and 24.6 ± 6.13, respectively. Both enzymes remained within the normal range, and no statistically significant intergroup differences were recorded ($P > 0.05$).

Ultimately, data from 60 diabetic patients were used for the final analysis. Upon completion of the three-month intervention period, patients in both groups responded to the items in the Michigan Neuropathy Screening Instrument (MNSI) to assess neuropathy symptoms. Additionally, post-intervention blood samples were collected to measure HbA1C levels (Figure 1).

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The data from the Kolmogorov-Smirnov test confirmed the normal distribution of the quantitative variables (P > 0.05); therefore, parametric tests were applied for data analysis. Based on the independent samples t-test, no statistically significant intergroup difference was found in terms of mean HbA1C levels before the intervention, indicating homogeneity between the groups (P = 0.91). The post-intervention data demonstrated a decrease in the mean HbA1C level in the intervention group in comparison to the placebo group. However, no significant intergroup difference was found (P = 0.17). Furthermore, intra-group analysis using the paired samples t-test demonstrated no significant changes in mean HbA1C levels in the pre-intervention and post-intervention phases in either the intervention or placebo group (P > 0.05) as shown in Table 2.

The findings from the independent samples t-test showed no statistically significant difference in the mean neuropathy scores between the two groups before the intervention (P = 0.22), confirming baseline homogeneity. However, post-intervention analysis revealed a statistically significant reduction in neuropathy symptoms in the intervention group in comparison to the placebo group (P = 0.001). Intragroup comparisons using the paired samples t-test demonstrated a significant decrease in the mean neuropathy score in the two groups after the intervention (P < 0.001). Notably, the magnitude of reduction was larger in the intervention group than in the placebo group, suggesting a more pronounced therapeutic effect of the *A. millefolium* extract (Table 3).

Table 1. Baseline characteristics of the patients in two groups

Demographic data		Herbal group	Placebo group	P-value
Age (years)	Mean ± SD	56.36 ± 7.82	57.41 ± 7.54	*0.60
Duration of disease	Mean ± SD	10.70 ± 4.48	11.0 ± 6.14	*0.83
Gender	Male (%)	10 (33.3)	9 (30.0)	*0.78
	Female (%)	20 (66.7)	21 (70.0)	
Marital status	Married (%)	28 (93.3)	29 (96.7)	***1
	Single (%)	6 (6.7)	1 (3.3)	
Educational Level	Under diploma (%)	23 (76.7)	16 (53.3)	**0.15
	Diploma (%)	5 (16.7)	11 (36.7)	
	Above diploma (%)	2 (6.7)	3 (10.0)	

*Mann-Whitney U
**Chi-square
***Fisher

Table 2. HBA_1C level at the baseline and endpoint in the herbal and placebo groups

Group	Herbal Group	Placebo group	*P-Value
Time	Mean ± SD	Mean ± SD	
Before Intervention	8.61 ± 1.61	8.56 ± 1.61	0.91
After Intervention	8.35 ± 1.86	8.56 ± 1.30	0.17
**P-Value	0.26	0.23	

*Independent T-Test (Inter-group Comparison).
**Paired T-Test (Intra-group comparison).

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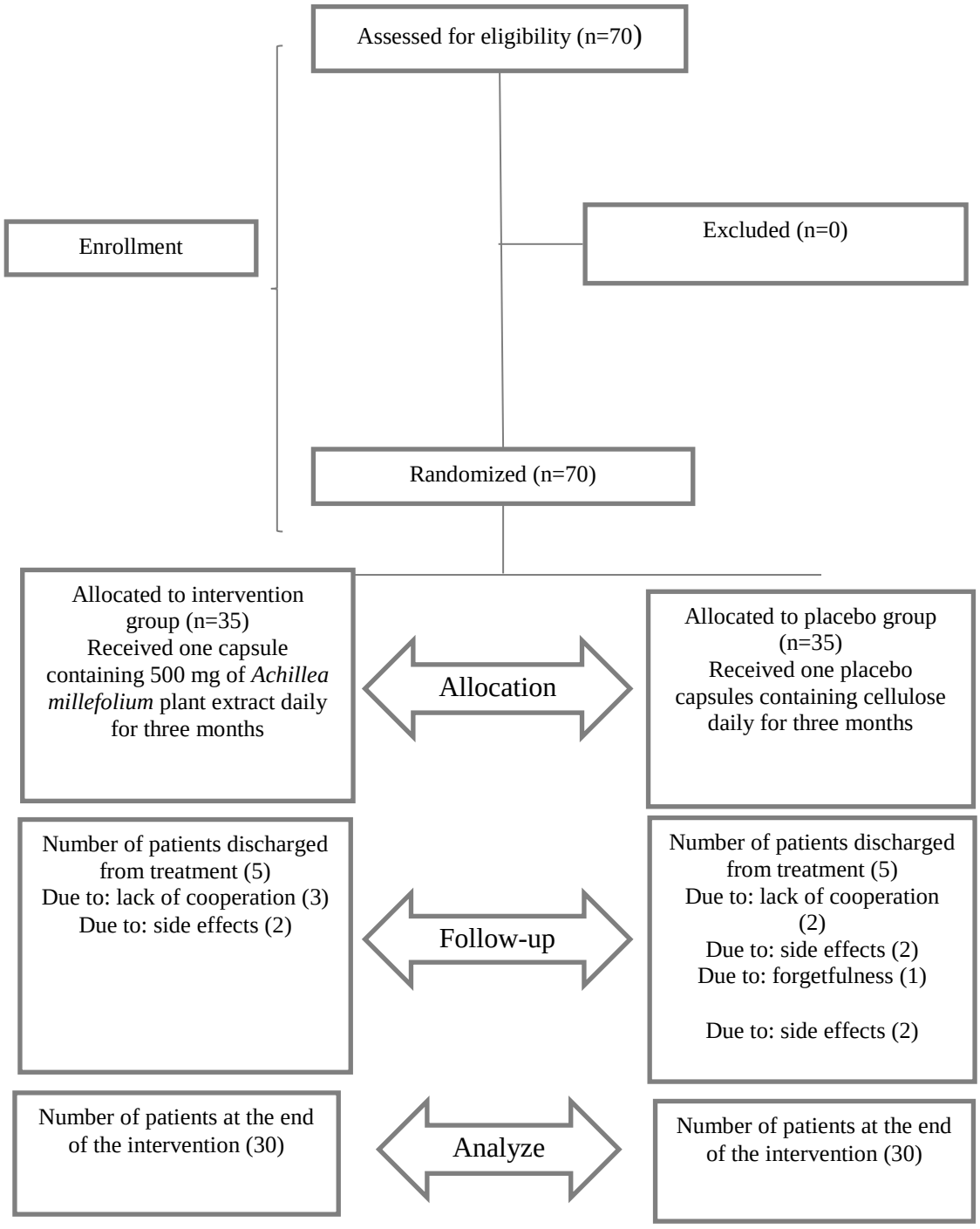

Fig. 1. Flowchart: Clinical trial chart

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Table 3. Neuropathy score at the baseline and endpoint in the herbal and placebo groups

Group	Herbal Group	Placebo group	*P-Value
Time	Mean ±SD	Mean ± SD	
Before Intervention	8.26 ±0.52	8.46 ±0.73	0.22
After Intervention	4.61 ± 2.07	6.30 ± 1.44	0.001
****P-Value**	< 0.001	< 0.001	

*Independent T-Test (Inter-group Comparison)
**Paired T-Test (Intra-group Comparison)

4. Discussion

The current study investigated the impact of oral supplementation with *Achillea millefolium* on hemoglobin A1C (HbA1C) levels and neuropathy-related symptoms in individuals with type 2 diabetes. Although there was a slight reduction in the mean HbA1C level among participants in the intervention group, this change did not reach statistical significance. While the antidiabetic properties of *A. millefolium* have not yet been confirmed in human trials, numerous animal studies have provided supporting evidence. For instance, Chávez-Silva et al. explored the antidiabetic activity of hydroalcoholic extracts of *A. millefolium* in hyperglycemic diabetic mice, demonstrating that the extract markedly enhanced insulin secretion in the treatment group compared to the control. Furthermore, oral glucose tolerance testing revealed a significant reduction in blood glucose levels among the treated mice [27]. Similarly, research conducted by Sadeghi et al. assessed the hypoglycemic potential of *A. millefolium* in both healthy and streptozotocin-induced diabetic rats. Their findings revealed a statistically significant decrease in blood glucose concentrations following administration of 100, 200, and 300 mg/kg doses of the extract in diabetic subjects, relative to controls. A comparable reduction was observed in normal mice treated with 300 mg/kg of the extract [34]. In another investigation, Karimi et al. also reported a significant decrease in blood glucose among diabetic rats treated with *A. millefolium* extracts, with results even surpassing those seen in animals receiving metformin [26]. In line with these animal-based studies, the current clinical trial observed a reduction in HbA1C levels within the treatment group, although this change lacked statistical significance. Possible explanations for these inconsistencies could include the relatively low dosage of *A. millefolium*, brief intervention duration, or limited sample size employed in this study.

The results of the current study demonstrated a statistically significant difference in neuropathy scores between the intervention and placebo groups following the treatment period. Specifically, participants in the intervention group exhibited a lower mean neuropathy score than those in the placebo group. Similarly, Ayoobi et al. investigated the use of *A. millefolium* extract as an adjunct therapy in patients with multiple sclerosis (MS). Their findings revealed that administering 500 mg of *A. millefolium* extract led to a significant reduction in patient disability, decreased brain plaque volume and inflammation, prolonged the interval between relapses, and lowered the annual relapse rate. These outcomes provide evidence for the herb's anti-inflammatory and neuroprotective effects [31]. In another study, Akramian Fard et al. evaluated the neuroprotective effects of an aqueous extract of *A. millefolium* in a rat model of Parkinson's

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disease induced by 6-hydroxydopamine (6-OHDA). Their results indicated that repeated administration of 1.4 and 2.8 mg doses of the extract improved motor function and muscle strength in the affected rats [35]. Additionally, Vazirinejad et al. assessed the influence of *A. millefolium* aqueous extract on experimental autoimmune encephalomyelitis (an animal model of MS) and its effect on serum cytokine profiles in C57BL/6 mice. Their findings showed that treatment with the extract led to reduced disease severity, diminished inflammatory reactions, and decreased demyelination in the EAE-induced mice [36]. Moreover, *A. millefolium* is rich in flavonoids such as quercetin, luteolin, and apigenin, which exhibit potent antispasmodic effects [37]. This antispasmodic activity may further contribute to the herb's efficacy in alleviating neuropathic pain.

The potential mechanism by which *A. millefolium* alleviates neuropathic pain may be attributed to its anti-inflammatory and antioxidant activities [38]. Oxidative stress is recognized as a key contributor to both inflammation and the development of diabetes-related complications, including neuropathic pain. Prior research has shown that *A. millefolium* is rich in essential oil constituents capable of mitigating chronic inflammatory conditions such as diabetic neuropathy. The herb's anti-inflammatory action appears to be mediated through the reduction of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), alongside an elevation in interleukin-10 (IL-10), an anti-inflammatory cytokine [38–39]. Furthermore, dietary supplements high in antioxidants have been associated with a lower risk of developing type 2 diabetes. These compounds also play a role in enhancing insulin sensitivity and preserving endothelial function in blood vessels [40].

In conclusion, the results showed that although the average neuropathy score declined in the placebo group following the intervention, the reduction was more pronounced in the intervention group. The observed improvement in the placebo group may be partially explained by the psychological effect of receiving a treatment, commonly referred to as the placebo effect. One limitation of the current study was the reliance on a questionnaire to assess neuropathy, which may be influenced by subjective perceptions. Therefore, future research should incorporate more objective methods, such as clinical evaluations, to measure neuropathic symptoms more accurately. Additionally, the absence of measurements for insulin levels, lipid profiles, and liver enzymes represents another limitation of this study.

5. Conclusion

The findings of this study suggest that the aqueous extract of *A. millefolium* may have a beneficial effect in alleviating neuropathic symptoms in patients with diabetes. In this trial, participants received a daily dose of 500 mg of *A. millefolium* extract. Accordingly, future research is recommended to explore the potential antidiabetic effects of higher dosages of the extract and to include evaluations of relevant biochemical markers associated with diabetes.

Author contribution

Author contributions Conceptualization, E.B., M.K., F.A., Z.J., and T.S; methodology, E.B., F.A., and T.S; software Z.J., and T.S; validation E.B., M.K., F.A., Z.J., and T.S; investigation, E.B., M.K., and T.S.; writing—

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original draft E.B., and T.S; writing—review and editing, E.B., M.K., F.A., Z.J., and T.S; visualization, M.K., F.A; supervision, T.S. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare there is no conflict of interest.

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