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Research Article

Impact of Resveratrol and Pharmaceutical Care on Type 2 Diabetes Mellitus and Its Neuropathic Complication: A Randomized Placebo Controlled Clinical Trial

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Background. Management of diabetic neuropathy (DN) is a challenging issue. Therefore, integration of pharmaceutical care provided by the clinical pharmacists with pharmacotherapy may provide multifaceted approach to target the management of hyperglycemia and diabetic neuropathic complication. This study aimed to evaluate the effects of resveratrol (Resv) and/or pharmaceutical care (PC) on glycemic control and amelioration of diabetes-associated neuropathic complications. *Patients and Methods*. A four-arm randomized placebo-controlled clinical trial assigned 120 patients from the Diabetes and Endocrinology Center in Sulaymaniyah City, Iraq. The patients were divided into four groups. The Resv group ($n = 30$) received 500 mg Resv capsules once daily. The Placebo group ($n = 30$) received placebo capsules. Resv + PC ($n = 30$) received Resv 500 mg capsules with PC. Placebo + PC ($n = 30$) received placebo capsule plus PC. The duration of the intervention was 90 days. Drug therapy problems (DTPs) have been utilized as an important domain in PC. Clinical signs, symptoms, and neuropathic abnormalities were assessed using the Michigan Neuropathy Screening Instrument (MNSI), Douleur Neuropathique 4 (DN4) questions, and nerve conduction studies (NCSs) of the lower-limb sensory and motor nerves. *Results*. 97 patients from all the groups completed the study. At baseline, 84% of the Resv, 87% of the Placebo, and 92% of each of Resv + PC and Placebo + PC groups, respectively, had at least one DTP. The provision of PC resulted in a dramatic reduction in the number of DTP. Resveratrol with PC significantly ameliorated hyperglycemic status, neuropathic signs, and symptoms, as evidenced by a decrease in MNSI and DN4 scores and improvement in electroneurographic parameters. *Conclusion*. These findings support the integration of the PC concept into a pharmacotherapy intervention; they also encourage supplementation of Resv with conventional diabetes therapy to emphasize on the importance of this herbal medicine with the provision of PC in the management of diabetes and its neuropathic complications. This trial is registered with NCT05172947.

1. Introduction

Diabetic neuropathy (DN) is a major microvascular complication of diabetes that results from prolonged periods of hyperglycemia, which damages fragile nerve fibers and blood vessel walls [1]. The common symptom of peripheral DN is symmetrical sensory pain that affects the lower limbs [2]. Other presentations of DN include numbness, pins, needles, and hot or burning sensation [3]. The neuropathic complication of diabetes is a heterogeneous and multifactorial disorder with multiple pathophysiological mechanisms [4, 5]. Several pathways have been identified as contributing

mechanisms to DN pathogenesis. This strongly encourages the use of multiple combined approaches, such as pharmacological and nonpharmacological interventions, in order to develop a multitarget treatment approach that ameliorates the hyperglycemic status and attenuates the destructive signaling pathways of individuals with diabetic neuropathy. Resveratrol (Resv) is a naturally occurring, plant-derived polyphenolic compound. Clinical studies have demonstrated that it exerts many effects, mainly anti-inflammatory, antioxidant, and analgesic effects [6–8]. Numerous *in vitro* and *in vivo* studies have demonstrated the glycemic control effect of Resv through several mechanisms [9]. These include decreasing blood glucose levels by improving glucose uptake, utilization, and storage, increasing insulin sensitivity, restoring abnormal insulin signaling pathways by inhibiting transcription of certain genes or inactivating proteins, promoting an increase in the pancreatic β-cell population, and triggering an increase in the secretion of insulin. Amelioration of advanced glycation end (AGE) product-induced dysregulated insulin signaling through the inhibition of AGE production and activities may also exert its antihyperglycemic effects through the activation of sirtuin-1 (SIRT1) [10–13]. The neuroprotective effect of Resv, its ameliorative effect on other diabetic complications rather than neuropathy [8], and most recently the alleviation of neuroinflammation in an animal viral infection model [14] provided encouraging evidence for the use of this molecule in the current clinical trial. Optimizing therapy for patients with diabetes is a difficult clinical task that requires considerable patient education and motivation. The involvement of clinical pharmacists in diabetes management centers can provide valuable services, help patients adhere to their therapeutic plans, and assist physicians in achieving better treatment outcomes [15].

Numerous studies have demonstrated the active role of clinical pharmacists in evaluating and intervening with patients with diabetic neuropathy, and they have concluded that the provision of pharmaceutical care (PC) showed an increase in the patient's knowledge about diabetic neuropathy and significantly decreased the patient's blood glucose level [16]. Studies on pharmacist interventions and PC have utilized a multifaceted approach to improve glycemic control such as detecting and resolving drug therapy problem (DTP), providing diabetic education, medication counseling, and many others [15, 17, 18]. From the literature, PC provided by clinical pharmacists plays a crucial role in the management of type 2 diabetes mellitus (T2DM) and in achieving therapeutic outcomes by monitoring drug therapy, educating the patient, encouraging medication adherence, and improving the quality of life [19].

Despite clinical developments and efforts to improve the quality of life of diabetic patients and the provision of PC in the treatment of diabetes and its complication [20], still the treatment of DN remains challenging, with no effective solution. Therefore, the current study was designed to use multidisciplinary approaches targeting the management of hyperglycemia and diabetic neuropathic complications. A thorough search of the relevant literature revealed that no study has been conducted to date to evaluate the cumulative effects of PC and Resv supplementation in ameliorating hyperglycemia- and diabetes-related neuropathic complications.

The role of pharmacist intervention in the one hand and the potential preclinical effect of Resv on the other hand encourage combining of these two approaches in the management of patients with diabetic neuropathy. Several preclinical studies on the resveratrol's protective effects on diabetic neuropathy exist [21, 22], and several suggested mechanisms have been postulated for the effect of resveratrol on amelioration of the complications accompanying diabetes, such as inhibiting the production of inflammatory factor interleukin-2 (IL-2), interleukin-β (IL-β), interleukin-8 (IL-8), tumor necrosis- α (TNF-α), and a decrease in the expression of inflammatory mediators, including prostaglandin-E2 and cyclo-oxygenase enzyme-2 (COX-2) [23, 24]. However, to the best of our knowledge, studies supporting the efficacy of Resv in clinical trials of diabetic neuropathy have not yet been conducted. Therefore, we hypothesized that a combination of Resv and/or pharmaceutical care might be valuable in managing diabetic neuropathy. The present study aimed to evaluate the effects of Resv and/or provision of PC on glycemic control and amelioration of diabetes-associated neuropathic complications at the Diabetic and Endocrinology Center in Sulaymaniyah City, Iraq.

2. Materials and Methods

2.1. Study Design. This study was designed as a four-arm, randomized, placebo-controlled clinical trial conducted from December 2021 to September 2022 at the Diabetes and Endocrinology Center, Directorate of Health, Sulaymaniyah City. The first two arms were resveratrol (Resv) and Placebo, and the other two arms were Resveratrol + Pharmaceutical care (Resv + PC) and Plecebo + Pharmaceutical care (Placebo + PC).

2.2. Ethical Consideration and Clinical Trial Registration. The study protocol was approved by the Ethics and Research Registration Committee of the College of Pharmacy/University of Sulaimani (Registration No: PH30-21 on 14 November 2021) and the Directorate of Health (DOH)-Ethical Committee. This study conformed to the provisions of the Declaration of Helsinki (revised 2013). Informed consent was obtained from all the patients. The study protocol was registered in the clinicaltrial.gov registration database https://clinicaltrials.gov/ct2/show/NCT05172947 with the ClinicalTrials.gov Identifier: NCT05172947.

2.3. Including and Excluding Criteria. Patients were enrolled in this study according to the following inclusion and exclusion criteria; this was based on a previous study with some modifications [25].

2.3.1. Including Criteria. Patients were included in the study if they had the following criteria:

(1) Men and women with type 2 diabetes aged 50–65 years
(2) Duration of diabetes ≥5 year
(3) HbA1c >7%
(4) Patients on oral antidiabetic agents alone or in combinations with insulin
(5) Patients presented with pain due to bilateral peripheral neuropathy
(6) Daily neuropathic symptoms must be present for at least six months, and the diagnosis is confirmed by a score ≥4 on the Michigan Neuropathy Screening Instrument (MNSI) [26, 27], Douleur Neuropathique 4 (DN4) [28], and abnormal nerve conduction study (NCS)
(7) The severity of pain when evaluated for the past 24 hours was ≥4 on the 10 cm visual analogue scale (VAS) at baseline without the use of analgesics for 48 hours

2.3.2. Excluding Criteria. Patients were excluded from the study if they had the following criteria:

(1) Type 1 diabetes mellitus
(2) Heart failure and a history of myocardial infarction
(3) Rheumatoid arthritis
(4) Lumber root abnormality or stenosis confirmed by MRI
(5) Pernicious anemia (Vitamin B12 deficiency)
(6) Thyroid, hepatic, and kidney problems
(7) Alcohol drinkers and psychological disorders
(8) Patients on antioxidant therapy or pentoxifylline within the last month
(9) Patients on analgesics such as pregabalin and anti-inflammatory drug

2.4. Enrollment, Randomization, and Intervention. The patients with peripheral diabetic neuropathy who attended the center were screened for eligibility, and those who met the inclusion criteria were enrolled in this study. The eligible patients were referred to a researcher (pharmacist) by a senior clinical endocrinologist. One neurologist confirmed diabetic neuropathy clinically and through a nerve conduction study. Participants were randomized using a simple technique. The researcher was well trained and acquainted with all procedures and examinations relevant to the assessment tools, including the MNSI and DN4.

Blinding was performed at the first visit and continued until the data analysis was completed. Eligible patients ($n = 120$) were randomly assigned to one of the following four groups:

(1) Resv group ($n = 30$): patients received a 500 mg Resv capsule orally once daily
(2) Placebo group ($n = 30$): patients received a placebo capsule orally once daily
(3) Resv + PC group ($n = 30$): patients received 500 mg Resv capsules orally once daily plus a PC process
(4) Placebo + PC group ($n = 30$): patients received a placebo capsule orally once daily plus a PC process

All groups received their conventional antidiabetic medications with the abovementioned interventions, and the duration of treatment was 90 days. The dose of resveratrol and the duration of the study were selected based on a previous study [29]. The components of PC were medication review for identification of DTPs, patient education and counseling, and partnership with other health professionals [30, 31]. All the patients voluntarily signed a written consent form before participating in the study.

2.5. Preparation of the Tested Medications and Blinding. The researcher formulated Resv (500 mg) capsules from Trans-resveratrol natural pure powder ≥98% (Apollo Healthcare Resources, Singapore) and placebo identical in shape, size, and color to the Resv capsules from carboxymethyl cellulose as a hard gelatin capsule, especially for this study. The participants and the researcher who dispensed the capsules and performed data collection were blinded to the contents of the containers. Furthermore, all participants were blinded to the randomization between the four groups, while the researcher was blinded to the non-PC intervention groups (Resv and placebo administration) until the analysis was completed. It was not possible to blind the clinical pharmacist responsible for providing pharmaceutical care process in the PC intervention groups (Resv + PC and Placebo + PC). Adherence was monitored through indirect methods such as pill counts and pharmacy refills. In addition, face-to-face interviews and behavioral and telephone-based interventions were conducted on a monthly follow-up basis.

2.6. Sample Size Estimation. The sample size was estimated based on a previous study by Movahed et al. and the mean, standard deviation, and differences between the means were calculated from the previous study [32]. Then, the following equation was used to calculate the sample size for each group:

$$n = \frac{\left(Z_{\acute{\alpha}} + Z_{\beta}\right)^2 * S^2}{(d)^2}, \quad (1)$$

where n is the sample size, S^2 is the standard deviation of the effect of the variable under study from the previous study (1.39), d is the difference the investigator wishes to detect = 1.0, $\acute{\alpha}$ is the conventional multiplier for alpha = 0.05 which is as shown in red font $Z_{\acute{\alpha}}$ will be 1.96, $1 - \beta$: for power of the study which is 80% so the $Z\beta = 0.842$.

$$n = \frac{(1.96 + 0.842)^2 * (1.39)^2}{(1.0)^2}, \quad (2)$$

where n (the estimated sample size for each group) = 30.

Therefore, 30 patients in each group were sufficient to achieve a statistically significant difference.

2.7. Outcome Measures. The primary outcome measure was to evaluate the clinical efficacy of Resv and PC on the severity of diabetic neuropathy and neuropathic pain using the MNSI for neuropathic signs and symptoms, DN4 for neuropathic signs and symptoms, and VAS for the severity of pain. All of the abovementioned parameters were measured on baseline day 30, 60, and 90 (i.e., up to 3 months). During MNSI assessment, responses of yes to items 1, 2, 3, 5, 6, 8, 9, 11, 12, 14, and 15 are each counted as one point. No responses to items 7 and 13 scored one point. Items 4 and 10 were not scored because they measured general asthenia and poor circulation, respectively [33].

Electroneurography (nerve conduction study) and serum neopterin levels were also evaluated on days 0 and after 90 days. A quantitative analysis of PC was performed, and the effect of PC on the main categories of drug therapy problems (DTPs) was recorded.

The NCS was performed by a specialist electromyographer who was blinded to the randomization of patients during the clinical assessment and NCS. Nerve conduction study was conducted on both the right and left lower limbs, focusing on three specific nerves: the motor peroneal nerve, motor tibial nerve, and the sensory sural nerve. The parameters of motor nerve were obtained from the compound muscle action potential (CMAP), and they are onset latency measured in millisecond (ms), amplitudes measured in millivolt (mV), and motor conduction velocity measured in meter per second (m/s). Sensory nerve parameters were obtained from the sensory nerve conduction action potential (SNAP), which consists of onset latency, amplitude, and conduction velocity. In addition, F-waves were recorded from the tibial nerves on both sides. NCS was performed using an EMG machine (CADWELL SIERRA WAVE, 4CH CA CE 100814-200)

The other outcome measures were to evaluate the clinical efficacy of Resv and PC on glycemic status through measurement of FBG levels at baseline and on days 30, 60, and 90 and mean change in HbA1c levels at baseline and after 90 days.

2.8. Statistical Analysis. Analyses were performed using GraphPad prism software, LCC, version 9.3. Categorical data are expressed as numbers and percentages, and continuous data are expressed as mean ± SD and median. Baseline and demographic data were analyzed using the Chi-squared test and ordinary one-way ANOVA to determine the statistical differences between different groups for categorical and continuous values, respectively. Two-way ANOVA repeated measure-mixed model followed by Tukey's multiple comparison test or Benforroni test was used for comparison between different groups in different timelines. A scatter dot plot diagram line at the median showing a cutoff value was used to demonstrate the response of the patients to the clinical assessments such as MSNI-History and Examination score and DN4 score of different groups at different timelines. P value <0.05.

3. Results

A total of 500 patients with peripheral diabetic neuropathy who attended the center were screened for eligibility, and 120 patients who met the inclusion criteria were enrolled in this study (Figure 1). Out of 120 patients, 97 completed the study as follows: Revs ($n = 25$), Placebo ($n = 23$), Resv + PC ($n = 25$), and Placebo + PC ($n = 24$).

Baseline demographic data for each group are shown in Table 1. There were no significant differences in demographic characteristics, including sex, age, body weight, BMI, and duration of disease, between the four groups with P values >0.05. Additionally, there were no significant differences in the glycemic parameters (FBG and HbA1c%), clinical neuropathic signs, and symptoms measured by MNSI-HI, MNSI-PE, DN4, and VAS scores between the four groups.

3.1. Quantitative Distribution of Pharmaceutical Care Intervention in the Resv + PC Group. In the Resv + PC group, 191 PC interventions were performed and recorded by the clinical pharmacist. Of these, 34% (65) were associated with DTPs, 56.5% (108) were associated with patient counseling and education, and 9.4% (18) were related to partnerships with other health professionals (Table 2).

3.2. Quantitative Distribution of Pharmaceutical Care Intervention in the Placebo + PC Group. In the Placebo + PC group, 192 PC interventions were performed and recorded by the clinical pharmacist. Of these, 31.7% (61) were related to DTPs, 57.8% (111) were associated with patient counseling and education, and 10.4% (20) were related to partnerships with other health professionals as shown in Table 3.

3.3. Baseline and Monthly Recorded Drug Therapy Problems (DTPs) in the Four Groups to Assess the Impact of Pharmaceutical Care on Them. The monthly fluctuations in the number of DTPs during 90 days of follow-up and/or of intervention medication profiles in the four groups of the present study are illustrated in Figures 2(a)–2(d). The results showed that in both Resv + PC and Placebo + PC groups, adding PC following pharmacist intervention resulted in a dramatic reduction in the number of DTP. Remarkable resolution and prevention of DTPs were achieved by a clinical pharmacist during the 90-day study period.

3.4. Impact of Resveratrol Supplementation with and without Pharmaceutical Care on Glycemic Parameters (FBG and HbA1c%). Figure 3 demonstrates a significant reduction (P value <0.01) in FBG in the Resv group after 90 days

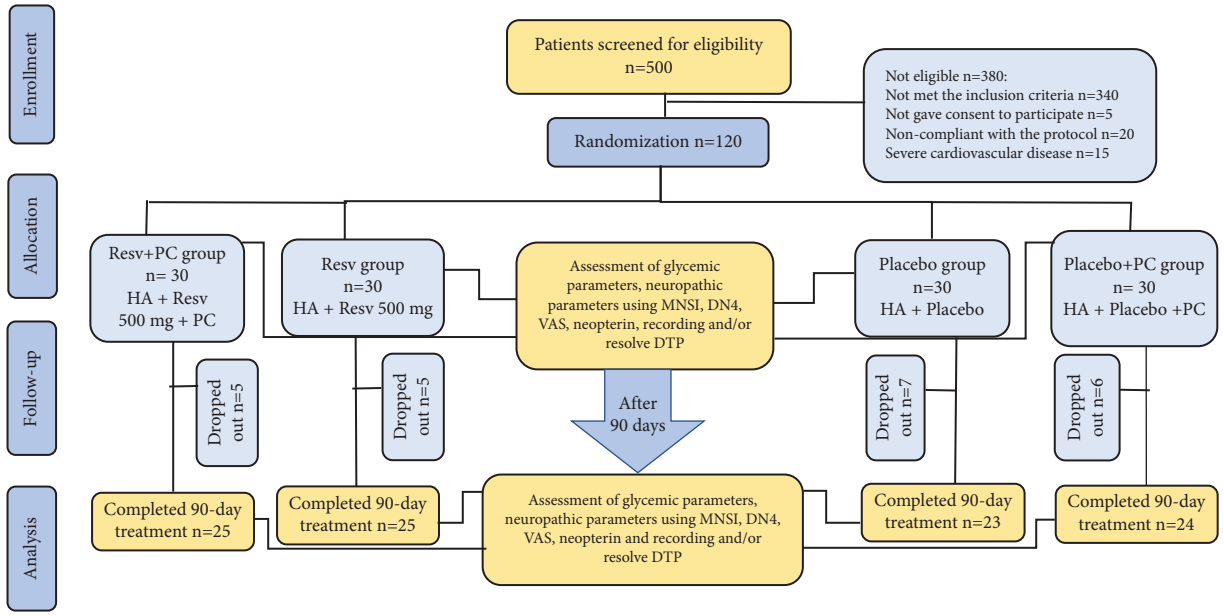

Figure 1: Flowchart for participant's enrollment, interventions, and outcome measures. *n*, number of patients; HA, hypoglycemic agent; PC, pharmaceutical care; Resv, resveratrol; DTP, drug therapy problem; MNSI, Michigan Neuropathy Screening Instrument for neuropathic signs and symptoms; DN4, Douleur Neuropathique 4 questions for neuropathic signs and symptoms; VAS, visual analogue scale for the severity of pain.

compared with both the baseline value and Placebo group. In the Placebo group, no change in FBG levels was observed at the end of 90 days when compared with the baseline. Furthermore, adding a PC process to placebo, as shown in the Placebo + PC group, resulted in a statistically significant reduction (P value <0.0001) in FBG levels after 90 days compared with both baseline values and the Placebo group. Moreover, adding the PC process to Resv supplementation, as shown in the Resv + PC group, led to a significant decrease in FBG levels (P value <0.0001) after 90 days compared with both baseline values and Placebo group.

Figure 4 demonstrates a significant reduction (P value <0.05) in HbA1c% in the Resv group after 90 days compared to the baseline value; however, this reduction was statistically nonsignificant with the Placebo group. In the Placebo group, a significant elevation in HbA1c% was observed at the end of 90 days compared with baseline. Furthermore, adding a PC process to the placebo, as shown in the Placebo + PC group, led to a statistically significant reduction (P value <0.01) in HbA1c% observed after 90 days compared to both baseline values and the Placebo group. Moreover, adding the PC process to Resv supplementation, as shown in the Resv + PC group, resulted in a further reduction in HbA1c% and in a statistically significant manner (P value <0.0001) after 90 days, compared with both the baseline value and Placebo group.

3.5. Impact of Resveratrol Supplementation with and without Pharmaceutical Care on Peripheral Neuropathic Symptoms Using the MNSI-HIS (Patients Interview). In the current study, the severity of DN and its improvement were assessed qualitatively using MNSI-HIS as a descriptive quality in three levels (no DN or mild when MNSI ≤4, moderate when MNSI score is between 5 and 6, and severe when MNSI ≥7) as shown in Table 4.

At the baseline level, all participants in the four groups had an MNSI-HIS score >4. In the Resv and Resv + PC groups on day 0, none of the patients had an MNSI <4, 20% had a moderate score, and 80% had a severe score. After 90-day intervention, 56% and 60% were in the no/mild limit, 36% and 28% in the moderate limit, and 8% and 12% in the severe limit, respectively. Therefore, a significant change (P value <0.0001) toward the improvement of neuropathic symptoms have been recorded after 90 days of treatment. In the Placebo group, MNSI-HIS values remained unchanged on days 0 and 90. Furthermore, adding PC to Placebo group, as shown in Placebo + PC group, an improvement in MNSI-HIS score toward the moderate range occurred, which led to a significant increase in the number of patients toward the moderate zone (MNSI-HIS = 5-6), but complete improvement toward MNSI-HIS <4 was not recorded.

3.6. Impact of Resveratrol with and without Pharmaceutical Care on Peripheral Neuropathic Signs Using the MNSI-PE (Physical Examination). The baseline scores for the MNSI-PE part in all the groups were similar, and there were no significant differences between them (P value >0.05). In the Resv group, a significant reduction in the median value was observed after 90 days compared to that at baseline. However, this reduction was not significant in the Placebo, Resv + PC, and Placebo + PC groups. In addition, a non-significant change was observed in both the Placebo and Placebo + PC groups after the 90-day intervention compared with the baseline. Furthermore, in the Resv + PC group,

Table 1: Demographic data and baseline characteristics of the recruited patients.

	Resv $n=25$	Placebo $n=23$	Resv + PC $n=25$	Placebo + PC $n=24$	P value
Variables					
Male	11 (44%)	9 (39%)	12 (48%)	9 (38%)	0.877
Female	14 (56%)	14 (61%)	13 (52%)	15 (62%)	
Age (years)	61.64 + 8.56	60 + 7.19	59.32 + 8.929	57.25 + 7.12	0.0612
Duration of diabetes (years)	15.8 + 4.85	16.3 + 4.06	16.76 + 3.734	16.46 + 3.73	0.0646
VAS	6.48 ± 1.98	7.6 ± 1.47	7.04 ± 2.01	6.68 ± 1.93	0.1635
MNSI-HIS (score)	9.6 ± 1.56	9.348 ± 1.58	9.36 ± 1.497	9.75 ± 1.68	0.7761
MNSI-PE (score)	4.652 ± 2.1	3.591 ± 1.64	3.620 ± 1.8	3.771 ± 2.32	0.224
DN4 score	8.0 ± 1.53	8.304 ± 0.97	7.920 ± 0.81	8.400 ± 0.96	0.357
Height (cm)	164.6 ± 8.18	157.8 ± 5.89	164.6 ± 7.767	161.9 ± 8.05	0.245
Weight (kg)	75.48 ± 13.33	72 ± 10.83	73.92 ± 12.94	74.54 ± 10.6	0.785
BMI	27.74 ± 3.87	28.82 ± 3.12	27.26 ± 4.652	28.5 ± 3.98	0.3914
FBG (mg/dl)	224 ± 81.67	213.4 ± 84.14	232.7 ± 80.52	247.4 ± 89.54	0.558
HbA1C %	10.18 ± 1.69	9.635 ± 1.89	10.36 ± 1.996	10.96 ± 2.392	0.128
Surgical history (yes)	12 (48%)	13 (56.5%)	12 (48%)	12 (50%)	0.998
Medications taken by the patients					
Metformin tab	16	16	12	12	0.350
DPP-4 inhibitor (sitagliptin or vildagliptin)	11	9	9	8	0.883
DPP-4 inhibitor + metformin (vildagliptin/metformin or sitagliptin/metformin) tab	12	10	11	13	0.897
Dapagliflozin or empagliflozin tab	6	6	7	9	0.745
Sulfonylurea (glimepiride or glibenclamide) tab	15	11	17	14	0.459
Insulin	16	12	11	15	0.531

Categorical data are expressed as number and percentage and continuous data as mean ± SD. Chi-square test and ordinary one-way ANOVA were used to determine the statistical differences between different groups for categorical and continuous values, respectively. P values <0.05 are considered as a significant statistically. DN4, Douleur Neuropathique 4; VAS, visual analogue scale; MNSI-HIS, Michigan Neuropathy Screening Instrument questionnaire history; MNSI-PE, Michigan Neuropathy Screening Instrument physical examination; PC, pharmaceutical care; DDP-4 inhibitor, dipeptyl peptidase-4 inhibitor; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin.

Table 2: Quantitative distribution of pharmaceutical care intervention in the Resv + PC group.

Components of PC	Subcategories in Resv + PC	*n* (%) subcategories	*n* (%) components of PC
Medication review for identification of DTPs	Indication	27 (14.13)	65 (34.03)
	Effectiveness	22 (11.51)	
	Safety	9 (4.71)	
	Compliance	7 (3.66)	
Patient education and counseling	Counseling regarding OHA	24 (12.56)	108 (56.54)
	Counseling regarding insulin administration	11 (5.75)	
	Counseling regarding hypoglycemic complications	24 (12.56)	
	Counseling regarding self-blood glucose monitoring	24 (12.56)	
	Counseling regarding foot care	25 (13.08)	
Partnership with other health professionals	Referral to specialist nurse	3 (1.57)	18 (9.42)
	Communicate with physicians	13 (6.80)	
	Referral to medical advice	2 (1.04)	
Total		191 (100)	191 (100)

Values are expressed as numbers and percentages (*n* (%)). DTP, drug therapy problem; PC, pharmaceutical care; Resv, resveratrol; and OHA, oral hypoglycemic agent.

Table 3: Quantitative distribution of pharmaceutical care intervention in the Placebo + PC group.

Component of PC	Subcategories in Placebo + PC	*n* (%) subcategories	*n* (%) components of PC
Medication review for identification of DTPs	Indication	25 (13)	61 (31.77)
	Effectiveness	23 (11.97)	
	Safety	5 (2.60)	
	Compliance	8 (4.61)	
Patient education and counseling	Counseling regarding OHA	24 (12.50)	111 (57.81)
	Counseling regarding insulin administration	15 (7.81)	
	Counseling regarding hypoglycemic complications	24 (12.5)	
	Counseling regarding self-blood glucose monitoring	24 (12.5)	
	Counseling regarding foot care	24 (12.5)	
Partnership with other health professionals	Referral to specialist nurse	2 (1.04)	20 (10.41)
	Communicate with physicians	14 (7.29)	
	Referral to medical advice	4 (2.083)	
Total		192 (100)	192 (100)

Values are expressed as number and percentage *n* (%). DTP, drug therapy problem; PC, pharmaceutical care; Resv, resveratrol; OHA, oral hypoglycemic agent.

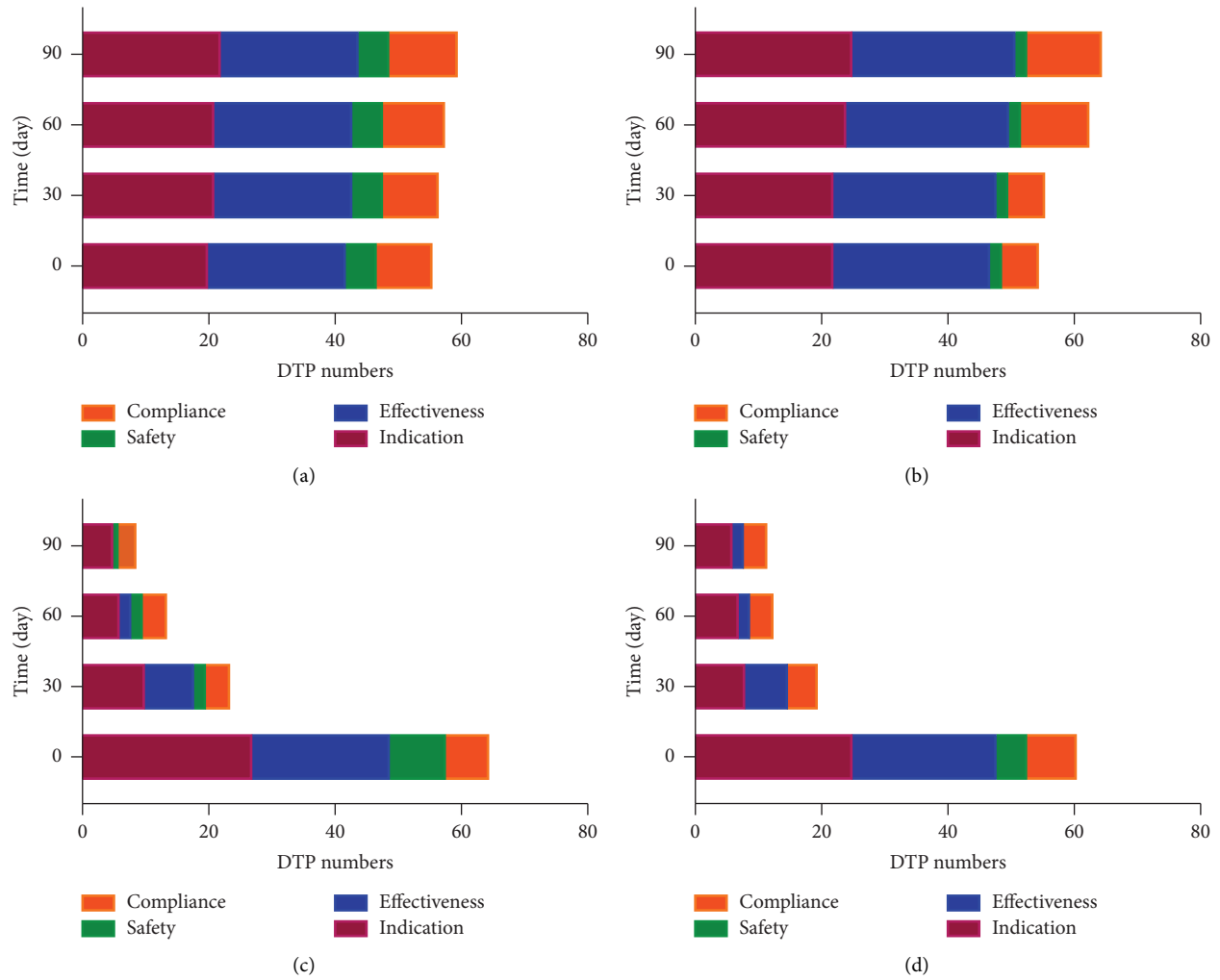

Figure 2: Monthly fluctuations in the number of DTPs main categories during 90 days. Follow-up and/or intervention medication profiles in the four groups: (a) Resv, (b) Placebo, (c) Resv + PC, and (d) Placebo + PC groups. Resv, resveratrol; PC, pharmaceutical care; DTP, drug therapy problem.

a significant reduction was observed in the median value after the 90-day intervention compared with the baseline value, Placebo group, and Placebo + PC group. In both the Resv and Resv + PC groups, the median value was reduced from 4.5 and 3 to 2.5 and 1, respectively, whereas no change in the median value was observed before and after the intervention in both the Placebo and Placebo + PC groups (Figure 5).

3.7. Impact of Resveratrol with and without Pharmaceutical Care on Peripheral Neuropathic Signs and Symptoms Using DN4. A significant reduction (P value <0.05) in the DN4 score in the Resv and Resv + PC groups after 90 days was observed compared with its baseline value and the score of the Placebo and Placebo + PC groups, whereas a comparable reduction was observed between them (Figure 6). Furthermore, in the Placebo group, no significant changes in the DN4 score were observed at the end of the 90 days when compared with its baseline. Adding a PC process to the placebo in the Placebo + PC group had no influence on the modifying the DN4-score toward neuropathic improvement. In both the Resv and Resv + PC groups, the median value of DN4 decreased from 8 to 5 and 4, respectively, whereas no change in the median value was observed before and after the intervention in both the Placebo and Placebo + PC groups.

3.8. Impact of Resveratrol with and without Pharmaceutical Care on Severity of Neuropathic Pain Using VAS-10 Pain Score. A statistically significant reduction (P value <0.05) in the VAS-10 score in the Resv and Resv + PC groups after 90 days was observed compared with both its baseline value and the Placebo group. In the Placebo group, a non-significant change (P value >0.05) in the VAS-10 score was observed at the end of 90 days when compared with baseline. Adding a PC process to placebo, as shown in the Placebo + PC group, did not result in a significant change (P value >0.05) in the VAS-10 score after 90 days, compared with both baseline values and the Placebo group. To be mentioned, a significant reduction in the VAS-10 score in both

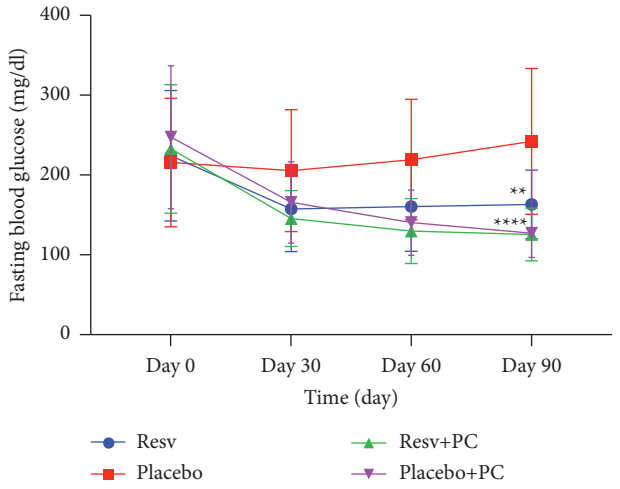

Figure 3: Monthly changes in the mean fasting blood glucose among the different groups. Two-way ANOVA repeated measure, mixed model, and multiple comparison were used and confirmed by Tukey's test. P values <0.05 are considered to be significant statistically different. **<0.01 and ****<0.0001. Resv, resveratrol and PC, pharmaceutical care.

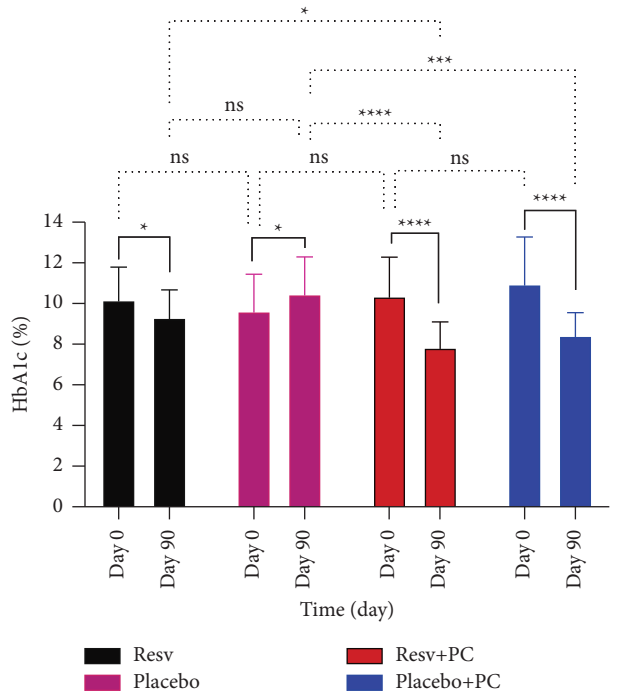

Figure 4: Effect of resveratrol with and without pharmaceutical care versus placebo on glycosylated hemoglobin (HbA1c) in patients with diabetic neuropathy. Two-way ANOVA repeated measure and multiple comparison were used and confirmed by Sidak's multiple comparisons test. P values <0.05 are statistically different. *<0.05, ***= 0.001 and ****<0.0001. Resv, resveratrol and PC, pharmaceutical care.

the Resv and Resv + PC groups was observed on day 30 and continued until the end of the study; the highest effect was observed on day 90 (Figure 7).

3.9. Impact of Resveratrol with and without Pharmaceutical Care on Electroneurographic Parameters (Nerve Conduction Study). NCS was performed for both the sensory (sural) and motor (peroneal and tibial) nerves. Based on the alteration in CAMP parameters such as a reduction of onset latency and increment of the amplitude, the response of the patients after 90-day of interventions has been categorized to "Improved," "Worsened," and "No change." It was assessed based on the changes from baseline (day 0) vs day 90 as "Improved," "Worsened," and "No Change". Motor and sensory NCS parameters were obtained bilaterally from the peroneal, tibial, and sural nerves. The final outcomes of the NCS in this study show that Resv supplementation with PC process resulted in improvement in electroneurographic parameters evidenced by increase in the number of patients in the "Improved" category as in terms of a shortening in latency and increase in amplitude and velocity of NCS after 90-day treatment (Figures 8 and 9).

Figure 10 represents F-wave latency for both right and left tibial nerves, and the responses that have recorded as "Improved" zone in left and right-tibial F wave were noticeable in Resv, Resv + PC, and Placebo + PC groups. However, higher improvement can be observed in Resv and Resv + PC as reflected by a higher number (%) of patients in the "Improved" zone after 90-day interventions. The results of the measurement of the parameters that are obtained from the SNAP (latency and amplitude for both the right and left sural nerves) showed no significant differences between all groups in terms of left sural nerve latency, left sural nerve amplitude, and right sural nerve amplitude (data not shown).

3.10. Impact of Resveratrol with and without Pharmaceutical Care on Neopterin Levels as an Inflammatory Biomarker for Diabetic Peripheral Neuropathy. The effect of Resv supplementation with or without PC versus Placebo with or without PC on the serum levels of neopterin showed that 500 mg/day Resv supplementation with or without PC for 90 days had no statistically significant effect on neopterin levels (P value >0.05) as shown in Table 5.

4. Discussion

In the present study, the impact of Resv and PC as a combined approach to alleviate neuropathic complications in T2DM has been investigated. Clinical pharmacists, as experts in pharmacotherapy, regularly engage in patient care and collaborate with other healthcare professionals to review medications for the identification, resolution, and prevention of DTPs. Consequently, in both groups that PC process implemented, the number of DTPs was remarkably reduced compared with the baseline. The monthly follow-up of patients strengthened the patients' bond with the clinical pharmacist, consequently generating greater confidence, which can be reflected by a greater commitment to therapies. The findings of the current study are in agreement with a previous study conducted on 71 T2DM patients in two groups: PC intervention and standard care groups. The

Table 4: Severity of diabetic neuropathy assessed by Michigan Neuropathy Screening Instrument (MSNI)-history scores of patients with diabetic neuropathic pain before and after administration of resveratrol with and without pharmaceutical care compared to placebo.

Duration (day)	Resv (n, %), total $n=25$			Placebo (n, %), total $n=23$			Resv + PC (n, %), total $n=25$			Placebo + PC (n, %), total $n=24$		
	≤4	5-6	>7	≤4	5-6	>7	≤4	5-6	>7	≤4	5-6	>7
Day-0	(0) 0^{a}	(5) 20^{a}	(20) 80^{a}	(0) 0^{a}	(4) 17^{a}	(19) 83^{a}	(0) 0^{a}	(5) 20^{a}	(20) 80^{a}	(0) 0^{a}	(1) 4^{a}	(23) 96^{a}
Day-30	(0) 0^{a}	(7) 28^{a}	(18) 72^{a}	(0) 0^{a}	(4) 17^{a}	(19) 83^{a}	(7) 28^{**b}	(8) 32^{a}	(10) 40^{**b}	(0) 0^{a}	(5) 21^{a}	(19) 79^{a}
Day60	(8) 32^{**a}	(12) 48^{a}	(5) 20^{*****a}	(0) 0^{b}	(5) 22^{a}	(18) 78^{b}	(15) 60^{*****a}	(7) 28^{a}	(3) 12^{*****a}	(0) 0^{b}	(4) 17^{b}	(20) 83^{b}
Day-90	(14) 56^{*****a}	(9) 36^{a}	(2) 8^{*****a}	(0) 0^{b}	(4) 17^{a}	(19) 83^{b}	(15) 60^{*****a}	(7) 28^{a}	(3) 12^{*****a}	(0) 0^{b}	(7) 29^{*a}	(17) 71^{*b}

Values are expressed as number (n) and percentage (%). Chi-square test was used to compare the different groups. Statistical significance was set at P value <0.05. *<0.05, **<0.001, and ****<0.0001. MNSI: Michigan Neuropathy Screening Instrument. *Significantly different compared to baseline within the same group ($P<0.05$); values with nonidentical superscripts (a, b) are significantly different among different groups within the same time ($P<0.05$). Resv, resveratrol and PC, pharmaceutical care.

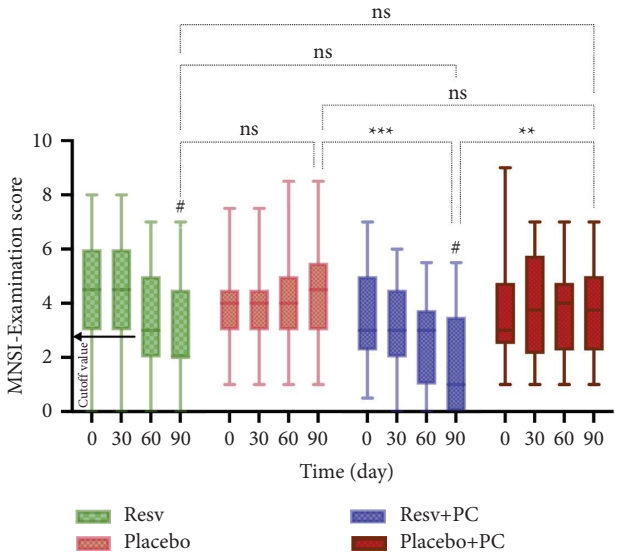

Figure 5: Effect of resveratrol with and without pharmaceutical care (PC) on neuropathic symptoms using Michigan neuropathy screening instrument (MSNI-examination) score shown as box and whiskers diagram. Line at median demonstrates MSNI-examination score of the patients with diabetic neuropathic symptoms from day 0 to day 90 of administration of resveratrol and placebo with and without pharmaceutical care. Two-way ANOVA repeated measure-mixed model followed by Tukey's multiple comparison was used for comparison between different groups. P value <0.05 was considered statistically significant. **<0.01 and ***<0.001. # denotes a statistically significant difference with the baseline. A cutoff value of MSNI-examination ≥2.5 consider as abnormal. Resv, resveratrol and PC, pharmaceutical care.

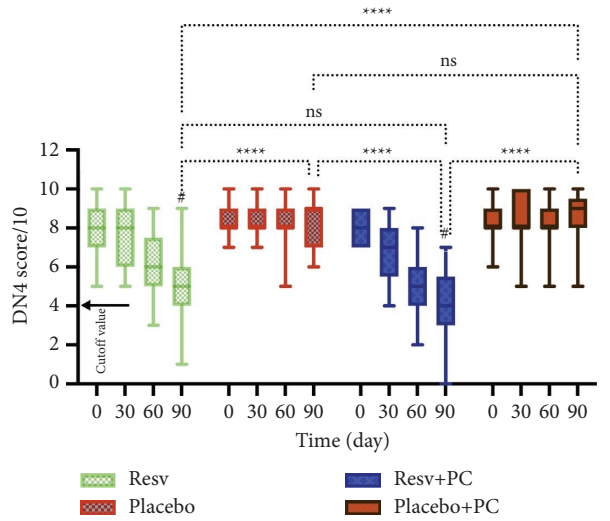

Figure 6: Effect of resveratrol with and without pharmaceutical care (PC) on neuropathic symptoms using Douleur Neuropathique 4 (DN4) questions score shown as box and whiskers diagram. Line at median demonstrates DN4 score of the patients with diabetic neuropathic symptoms from day 0 to day 90 of administration of resveratrol with and without pharmaceutical care. Two-way ANOVA repeated measure-mixed model followed by Tukey's multiple comparison was used for comparison between different groups. P value <0.05 was considered statistically significant. *<0.05 and ****<0.0001. # denotes a statistically significant reduction with the baseline. A cutoff value of DN4 ≥4 consider as abnormal. Resv, resveratrol and PC, pharmaceutical care.

results showed that after 12 months of PC provision, there was a significant reduction in the DTPs [34].

The potential effect of Resv on the reduction of FBG and HbA1c% levels in this study is comparable with that of two previous clinical trials. The first trial used Resv (250 mg/day) along with their oral antidiabetic medications for 90 days [35], and the second one used 1 g/day of Resv for 45 days [32]. These studies with the current one provide convincing evidence of the glucose-lowering effect of Resv. However, the current findings were not in agreement with those of a clinical trial conducted on 14 patients with T2DM who received 500 mg Resv or placebo twice daily for five weeks (35 days), and the results showed that there was no statistically significant effect on fasting and HbA1c% reduction as glycemic parameters [36]. This finding might be related to the differences in the study duration, which was longer in the current study than in the previous study.

The role of PC in the context of lowering glycosylated hemoglobin was superior, as depicted in Resv + PC and Placebo + PC, compared to Resv alone. This finding provides interesting evidence of the importance of the impact of PC on glycemic control. Although in the current study, the reduction of HbA1c levels in the Resv group was less than that of the PC group, the improvement in the neuropathic signs and symptoms, which were assessed by MNSI, DN4, and VAS, was comparable to those in the Resv + PC group.

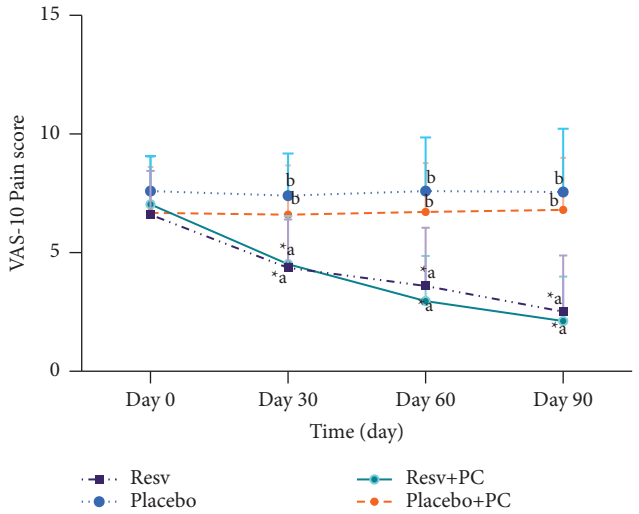

Figure 7: Effect of resveratrol with and without pharmaceutical care versus placebo on pain expressed as visual analogue scale (VAS) in patients with diabetic neuropathy. Two-way ANOVA repeated measure and multiple comparison were used and confirmed by Tukey's test. *Significantly different compared with baseline within the same group; values with nonidentical superscripts (a and b) are significantly different among different groups within the same timeline. P values <0.05 are considered statistically different. Resv, resveratrol and PC, pharmaceutical care.

This is because fluctuations in FBG and the two-hour postprandial plasma glucose levels are directly related to the risk of vascular complications rather than HbA1c in patients with T2DM [37]. The pathogenesis of DN is multifactorial, and it results from a combination of factors such as prolonged high blood glucose levels, inflammation, and oxidative stress, and addressing all these factors simultaneously can be challenging that necessitates combination of various approaches.

The reduction in both FBG and HbA1c% levels due to the provision of PC in this study is consistent with two randomized controlled clinical trials, in which the provision of PC resulted in a significant reduction in both FBG and HbA1c levels compared to the control group patients [31, 38].

In the present study, Resv significantly reduced clinical neuropathic signs and symptoms, as shown by both neuropathic pain scales (MNSI and DN4). The exact mechanism of this improvement may be due to the antioxidant, anti-inflammatory, analgesic, and glucose-lowering properties of Resv, which have been found to be effective in diabetic patients [39, 40]. The most proposed molecular mechanism by which hyperglycemia induces complications in diabetes is increased oxidative stress [41] that enhance inflammation; then, both processes may underlie a painful condition [42]. The Nrf2 and NF-κB pathways are important pathways that regulate the intracellular redox response and inflammatory balance. A previous study suggested that Resv modulates NF-κB by increasing Nrf2 activation and the expression of antioxidant enzymes, which might be responsible for the neuroprotective effect of Resv in DPN [43]. Various studies have suggested that the neuroprotective activity of Resv is attributed to its antioxidant and anti-inflammatory properties [44]. Resv has been reported to inhibit lipid peroxidation and neuronal cell death induced by oxidative stress and to enhance various antioxidant enzymes [45]. These effects can be attributed to its properties as potent scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [46]. Another animal study demonstrated that Resv attenuated oxidative stress, which led to protection against oxidative damage in DN [47].

In this study, the PC process led to a significant increase in the number of patients toward the moderate zone (i.e., MNSI-HIS = 5-6) of improvement; however, complete improvement toward MNSI-HIS <4 has not been reported. This finding is not consistent with a previous study conducted by Hayat et al. in which a significant reduction in the signs and symptoms of DN was observed in the pharmacist's intervention group after one year of the study [48]. This discrepancy in results may be due to the shorter duration of the intervention in the present study.

To be mentioned, during Resv supplementation with PC, a highly significant improvement occurred in the MNSI and DN4 scores, which can be explained by the necessity to target the pathogenesis of the disease by Resv to restore and recover the abnormalities of this deliberate complication of diabetes. This finding complies with the concepts of other studies that support targeting the underlying pathology of the disease rather than the modulation of the symptoms of the disease [25, 49].

Furthermore, Resv had a significant effect on reduction of VAS-10 pain scores. The suggested mechanism of Resv in the amelioration of pain was elucidated by the reduction in the production of prostaglandins [50], via various voltage-dependent ion/ligand-gated channels, neurotransmitter receptors, and inflammatory signaling cascades [51]. The P2X7 and P2X3 receptors in the dorsal root ganglia (DRG) are associated with inflammatory and neuropathic pain [52]. Previous animal study indicated that Resv might decrease the upregulated expression of the P2X7 receptor and inhibit the transmission of nociceptive signaling, which might decrease the sensitization of neurons in the DRG [53]. Another previous study in animal models demonstrated that Resv prevents P2X3 upregulation, and ERK phosphorylation in the DRG may play an analgesic role in neuropathic pain signal transduction [54]. Furthermore, intracellular Ca2+ signaling is usually significantly enhanced during pain process [55]. Reduced concentration of calcium ions in the neurons can produce analgesic effects [56]. A previous study in an animal model demonstrated that Resv inhibited calcium channels, which led to reduced intracellular calcium concentrations and produced an antinociceptive effect [57].

On the other hand, the impact of the PC intervention on the pain score displayed a nonsignificant change in the VAS-10 score in the Placebo + PC group. However, a highly significant improvement in neuropathic pain was recorded using VAS in the Resv + PC group. This could be explained by the potential abovementioned antinociceptive mechanisms of Resv. Therefore, PC needs to be provided for a long-term option.

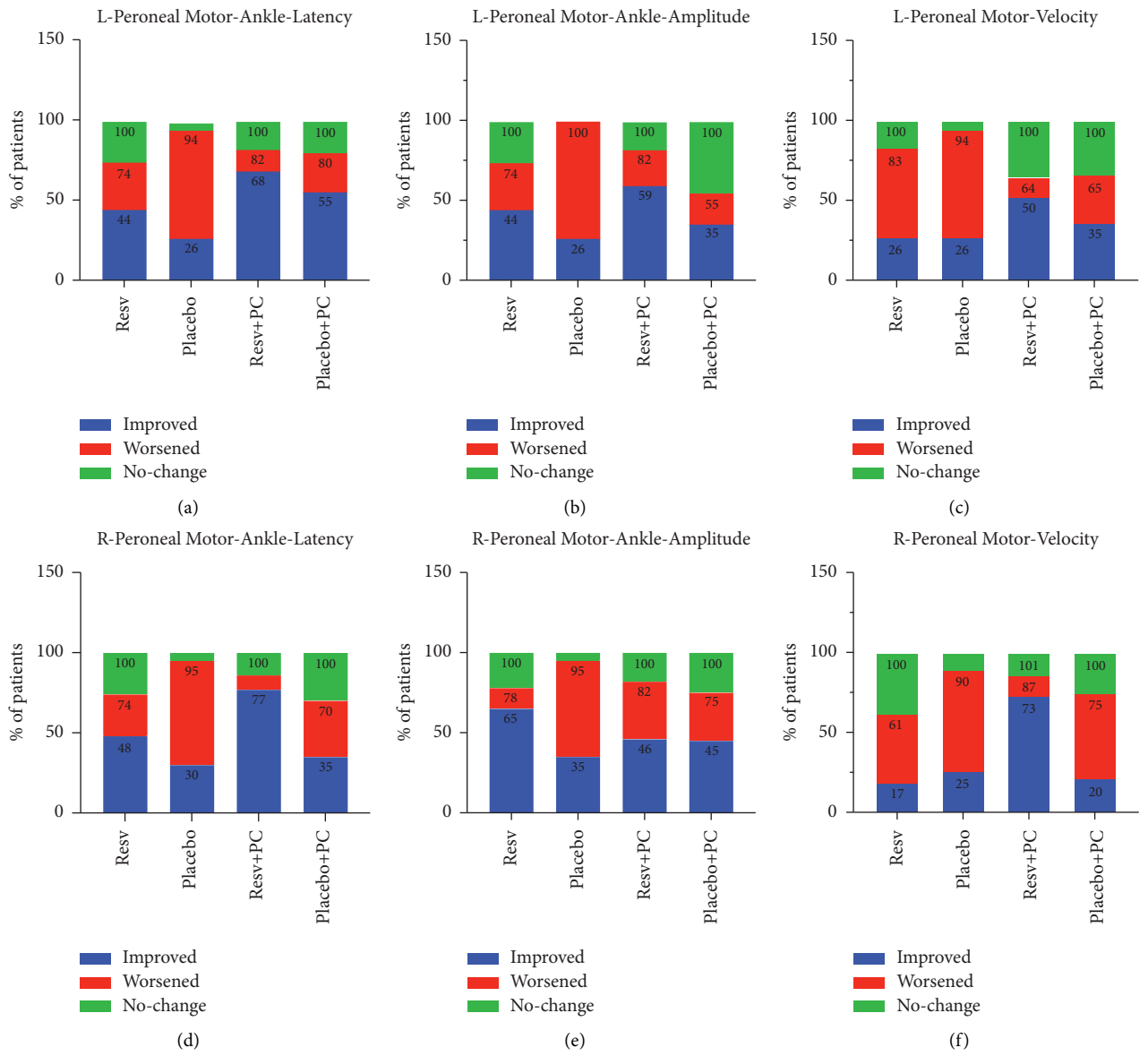

Figure 8: Nerve conduction study (NCS) of peroneal motor nerve at ankle. Latency and amplitude were measured for left (L) (a–c) and right (R) (d–f) peroneal nerve. The changes in the NCS at day 90 after interventions were defined as "Improved," "Worsened," and "No change" category. The data show the percentage of patients for each level in different groups. Resv, resveratrol and PC, pharmaceutical care.

In the current study, a nonsignificant change in serum neopterin level was observed after 90 days of intervention. Systemic inflammation in T2DM patients who are on oral antidiabetic agents (as single or combination therapy) usually leads to elevation of neopterin levels to a greater extent than in T1DM patients who are on insulin therapy [58]; therefore, this may be a reason why Resv with and without PC did not exert a significant effect on neopterin levels in the short duration of this study. Thus, further studies are recommended to examine neopterin for a longer duration as well as in T1DM.

The principal findings in the NCS were that Resv resulted in the improvement of most of electroneurographic parameters which was evidenced by increase in the number of the patients in the "Improved" zone after 90-day treatment. Multiple mechanisms underlying its efficacy in restoring and improving nerve function have been postulated in various preclinical studies. An in vitro study showed that Resv was effective in promoting the release of neurotrophic factors such as brain-derived neurotrophic factor and glial-derived neurotrophic factor [59]. The other suggested mechanism that was clarified in an animal model of chronic constriction nerve injury might be related to the improvement of locomotor performance through the restoration of insulin-like growth factor-1 levels as a neurotrophic factor [60].

On the other hand, the provision of the PC process in the Placebo + PC group in the present study exerted a comparable/or greater impact on the improvement of the NCS parameters compared to the Resv group. This can be explained by PC's significant role in glycemic control, which

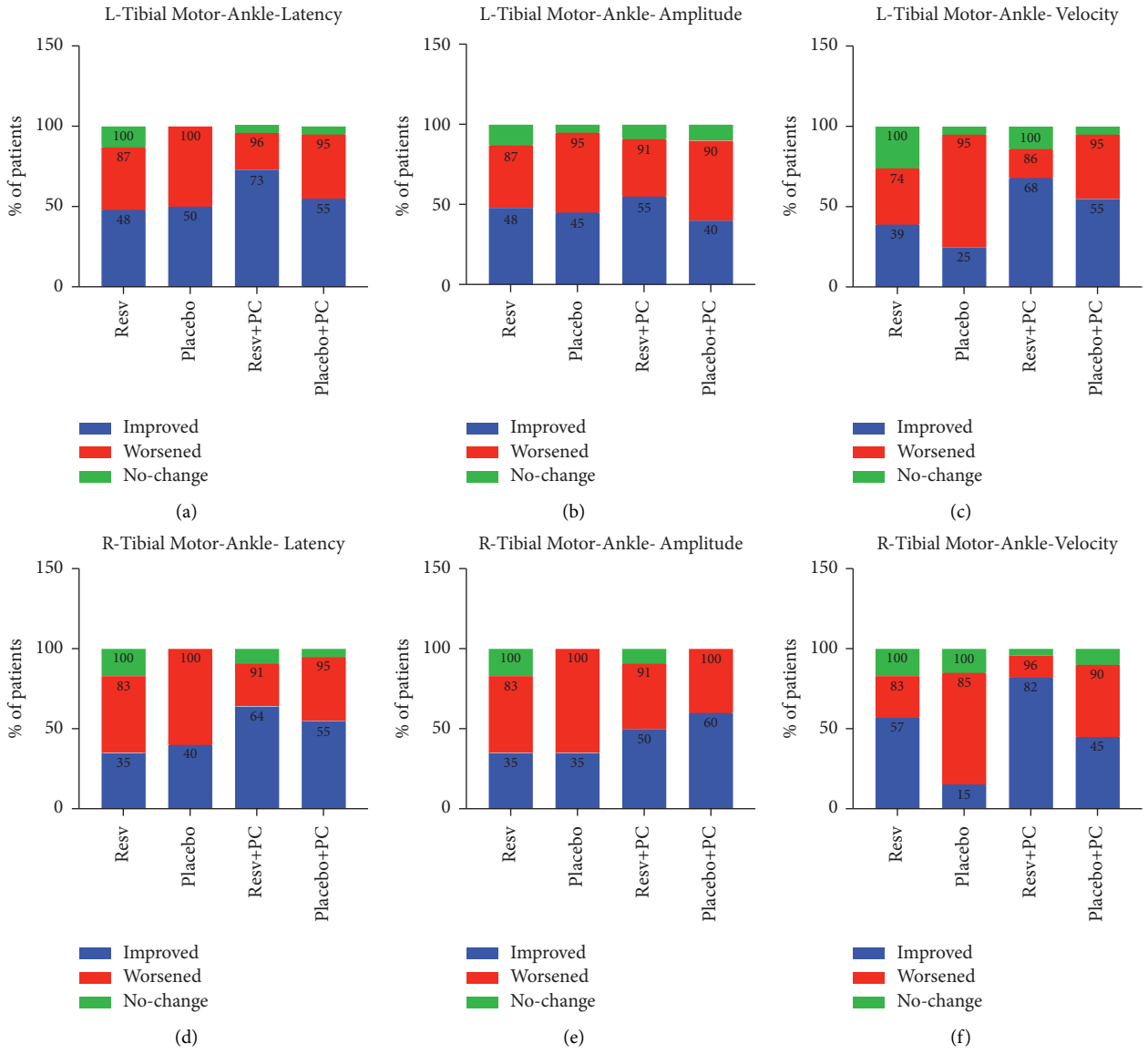

Figure 9: Nerve conduction study (NCS) of tibial motor nerve. Latency and amplitude were measured for left (L) (a–c) and right (R) (d–f) tibial motor nerve. The changes in the NCS at day 90 after interventions were defined as "Improved," "Worsened," and "No change" category. The data show the percentage (%) of patients for each level in different groups. Resv, resveratrol and PC, pharmaceutical care.

consequently halts oxidative stress and further nerve damage. In addition, PC played a significant role in improving the quality of life of patients (data not shown), and consequently might have contributed to the improvement in nerve function through better disease control and encouraging physical activity by the patient.

In addition, the combination of the PC process with Resv in the Resv + PC group led to further improvement in nerve function. It seems that a multidisciplinary approach is necessary to be applied in diabetic centers, as it is safe, effective, and easy to be implemented.

An interesting aspect of this study is that the greater improvement in CAMP for both bilateral peroneal and tibial nerves, as well as the tibial-F-wave (objective data), matches the improvement of clinical symptoms and neuropathic pain in MNSI and DN4 scores in diabetic patients (subjective data). Therefore, improvements in neuropathic signs and symptoms assessed using various tools support neurophysiological studies (i.e., nerve conduction studies).

Furthermore, we observed a greater improvement in motor nerve conduction than in sensory nerve conduction, which is inconsistent with a study that investigated a combination of two potent antioxidants. [61]. The reason might be due to differences in sensory and motor nerve structures; the key element in this discrepancy is Schwann cells. Following peripheral nerve injury, they de-differentiate in order

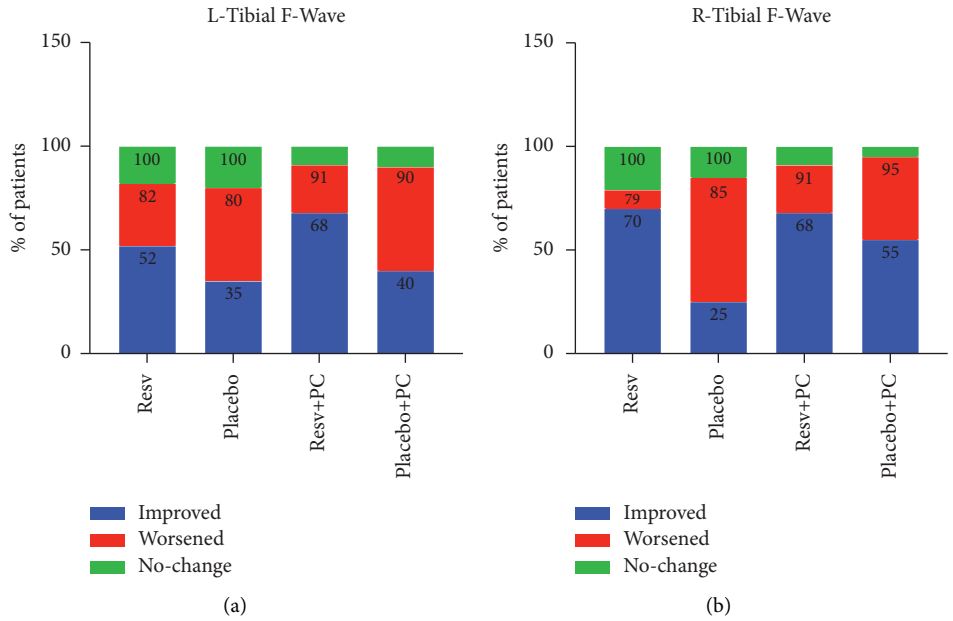

Figure 10: F-wave study of tibial motor nerve. F-wave latency was measured for left (L) (a) and (R) right (b) tibial motor nerve. The changes in F-wave latency at day 90 after interventions was defined as "Improved," "Worsened," and "No change" levels. The data show the percentage (%) of patients for each level in different groups. Resv, resveratrol and PC, pharmaceutical care.

Table 5: The effect of resveratrol supplementation and pharmaceutical care versus placebo on neopterin levels in diabetic patients with neuropathic complications.

Time	Group			
	Resv ($n = 25$)	Placebo ($n = 23$)	Resv + PC ($n = 25$)	Placebo + PC ($n = 24$)
Neopterin (nmol/L) day-0	4.657 ± 0.620	4.478 ± 0.668	4.630 ± 0.675	4.522 ± 0.853
Neopterin (nmol/L) day-90	4.511 ± 0.652	4.107 ± 0.648	4.399 ± 0.688	4.280 ± 0.564

Values are presented as mean ± SD; the data show that there are no significant differences in neopterin levels between resveratrol supplementation and pharmaceutical care versus placebo and pharmaceutical care on neopterin level after 90-day interventions (P value >0.05). Two-way ANOVA repeated measures analysis of variance (ANOVA) and multiple comparisons were performed and confirmed using Tukey's test. n, number of patients; Resv, resveratrol; PC, pharmaceutical care.

to secrete survival and growth-promoting factors for regenerating neurons [62]. Alternately, because motor nerves tend to have greater myelination, it is possible that motor nerve provide a more Schwann cell-rich environment for regeneration than sensory. In addition, the motor nerve has larger diameter but fewer fibers in comparison to the sensory nerve; these larger endoneurial tubes may mechanically provide a more favorable size conduit for nerve regeneration than the smaller sensory endoneurial tube [63]; therefore sensory nerves might require a longer duration of Resv treatment to obtain clear results.

4.1. Limitations and Strength of the Study. The current study had several limitations, including the small sample size and the short duration of therapy. On the contrary, the strength side of this study was that it was a triple-blind, randomized, placebo-controlled clinical trial. The study also provided convincing objective and subjective evidence for the adjuvant use of Resv in the management of diabetic patients to improve neuropathic complications. As far as is known, the present study is the first clinical trial to highlight the effects of Resv with and without PC in ameliorating diabetic neuropathic complications, using both clinical and electroneurographic assessments.

5. Conclusion

Resveratrol was effective in ameliorating hyperglycemia, neuropathic pain, and abnormal NCS in patients with diabetic neuropathy. In addition, pharmaceutical care services have a positive impact on the improvement of the glycemic status and neuropathic complications. Therefore, the findings of the present study support the integration of the concept of pharmaceutical care services into multidisciplinary work and encourage the use of resveratrol with other conventional diabetic therapies. The combination of these different strategies led to improvements in both subjective and objective parameters in diabetic patients with neuropathic complications.

Data Availability

All the individual data of the participants that have been collected during the trial and underline the results have been

included in the study. However, the study protocol, informed consent, clinical trial protocol, and ethical and research registration approval of the university can be provided through the contact to the corresponding author.

Ethical Approval

The Ethics and Research Registration Committee of the College of Pharmacy/University of Sulaimani (Registration No: PH30-21 on 14 November 2021) and the Directorate of Health (DOH)-Ethical Committee approved the protocol of the study. The study protocol was also registered in the clinicaltrial.gov registration database https://clinicaltrials.gov/ct2/show/NCT05172947 with the ClinicalTrials.gov Identifier: NCT05172947.

Consent

All participants in this study voluntarily signed a written consent form before enrollment.

Conflicts of Interest

The authors declare that they have no conflicts of interest in this work.

Authors' Contributions

M. Amin GS contributed in the patient's screening, recruitment, pharmacist interventions, data collection, assessment, and analysis and reviewed the manuscript. Marouf BH conceptualized the research design, analyzed the data, wrote the first draft of the manuscript, and completed the final version. Namiq HS performed nerve conduction study, involved in patient screening and recruitments and clinical patient follow-up, and reviewed the manuscript. Salih JM contributed in screening and recruitment of the patient, data collection, and clinical follow-up of the patients and reviewed the manuscript. All the authors reviewed and approved the final draft.

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