

## The Effects of Resveratrol Supplementation on the Quality of Life of Diabetic Patients with Neuropathy: A Small Randomized Clinical Trial

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### Abstract

Diabetic neuropathy exerts a considerable decline in the level of patient's well-being. The main approaches to hamper the progression of diabetic complications and improve patient's life quality are controlling the glycemic levels. Supplementation of appropriate anti-inflammatory and anti-oxidants such as resveratrol may be effective in the management of diabetic complications. The aim of this trial was to assess resveratrol's impact on improving quality of life of the patients with the neuropathic complication of diabetes. Sixty-one patients with diabetic neuropathy who attended the Center for Diabetes and Endocrinology, Directorate of Health/Sulaimani City, were recruited in this double blinded placebo-controlled trial. Patients were randomized into the resveratrol group (n=31); who received a 500mg resveratrol capsule once daily concomitantly with the conventional hypoglycemic agents for three months, and the placebo group (n=30). From each group 25 patient completed the study. The duration of the study was ten months, it started on December 2021 till September 2022. The quality of life (QoL) of the patients was estimated utilizing RAND 36-Item Health Survey version-1 questionnaire (RAND 36). Fasting blood glucose levels were analyzed at the baseline and on the last day of the 3<sup>rd</sup> month. There was a significant decrement ( $p < 0.001$ ) in the fasting serum glucose level of the patients supplemented with resveratrol at the end of the 3<sup>rd</sup> month, in comparison with the patient using the placebo. There was also a significant improvement in patient's severity of pain ( $p < 0.001$ ) as shown in the bodily pain score of the RAND 36 scale and a remarkable ( $p < 0.05$ ) improvement in physical functioning, physical health, social functioning, emotional-well-being, energy/fatigue, and health change subscales of the questionnaire. The study concluded that resveratrol has a positive effect on reducing pain associated with diabetic neuropathy and improving the overall QoL of the patient. This could be related to the dramatic reduction in the glycemic status and amelioration of severity of pain by resveratrol.

**Keywords:** Diabetic neuropathy, Life quality, Pain, RAND 36, Resveratrol.

### إضافة المكمل الغذائي ريسفيراترول يحسن جودة الحياة المرضى السكري من النوع الثاني الذين

#### يعانون من اعتلال العصبي السكري – دراسة سريرية أولية

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### الخلاصة

اعتلال الاعصاب المحيطية المرافقة لمرض السكري يؤدي الى انخفاض كبير من جودة الحياة للمرضى المصابين بالسكري، لذلك العلاجات المستهدفة لهذا المرض هي السيطرة على نسبة السكر في الدم وتخفيض التهاب الاعصاب والاجهاد التأكسدي والألم الناجم عن ارتفاع السكر في الدم من اجل إعاقة تطور مضاعفات مرض السكري كالاختلال العصبي السكري وبالتالي تحسن جودة الحياة لديهم. حيث ان تناول المكملات الغذائية المضادة للالتهابات والاكسدة كريسفيراترول ذات القيمة العالية في معالجة مضاعفات المرض السكري.

كان الهدف من هذه الدراسة هو تقييم تأثير المكمل الغذائي الريسفيراترول في تحسين جودة الحياة للمرضى الذين يعانون من اعتلال العصبي السكري مقارنة بالادوية الوهمية (placebo). هذه الدراسة عبارة عن تجربة سريرية عشوائية مزدوجة التعمية أجريت على 61 مريض يعانون من اعتلال العصبي السكري. حيث تم تقسيم المرضى الى مجموعتين: المجموعة الريسفيراترول (العدد=31)، تناولت كبسول ريسفيراترول 500 ملغم مرة واحدة باليوم مع الادوية السكري التقليدي الموجودة لدى المريض لمدة ثلاثة أشهر. والمجموعة الثانية (العدد=30) تناولت الدواء الوهمي. تم تقييم جودة الحياة المرضى بالاستخدام الاستنبابان جودة الحياة RAND 36 وتم تحليل مستوى جلوكوز الدم الصائمي في الدم في بداية التجربة وفي اليوم الأخير من الشهر الثالث. لوحظ من النتائج بان هناك انخفاض كبير في مستوى جلوكوز الدم الصائمي ( $p\text{-value} < 0.001$ ) في مجموعة الريسفيراترول مقارنة مع مجموعة الدواء الوهمي (placebo). كان هناك تحسن كبير في شدة الألم لدى المرضى كما هو موضح في جزء الألم الجسدي من الاستنبابان RAND 36. وكذلك كان هناك تحسن كبير في الجزء الوظيفة الجسدية والصحة البدنية والوظيفة الاجتماعية والرفاهية العاطفية او الصحة العقلية و الإرهاق. استنتجت هذه الدراسة بان ريسفيراترول هو البوليفينول الفعال الذي له تأثير في تقليل الألم في مرض اعتلال العصبي السكري مع تحسين الشامل لجودة الحياة المريض.

الكلمات المفتاحية: اعتلال العصبي السكري، ، جودة الحياة، الألم، RAND 36، ريسفيراترول.

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## Introduction

Diabetic neuropathy exerts a considerable decline in the level of patient's well-being. It is associated with uncontrolled glycemic status, metabolic dysfunction, hyperlipidemia, destruction of the nerve fibers and the wall of their microvascular compartment<sup>(1,2)</sup>. It is regarded as one of the costly complications linked to diabetes.

It affects about 50% of patients with diabetes<sup>(3)</sup>. Common symptoms include sensation of burning, tingling, numbness, pain or weakness beginning in the distal lower extremities progressing to more severe symptoms of neuropathic pain<sup>(4,5)</sup>. Although the symptoms may be not permanent but can be exhausting, result in depression, sleep problems and generally worsen the quality of life (QoL)<sup>(6)</sup>. It is obvious that diabetic patients with peripheral neuropathy are more prone for developing tissue destruction, diabetic foot ulcers, and even foot amputation<sup>(7)</sup>.

Nowadays, QoL is regarded as one of the most crucial components of patients' lives that are affected by many diseases including diabetes<sup>(8)</sup>. It is, therefore, well accepted as one of the important targets in the treatment of diabetes<sup>(9)</sup>. In addition to poor glycemic control, diabetic neuropathy complications are related to the impairment of the anti-oxidant status and inflammatory process.

Despite huge progression in the therapies for treatment of neuropathy complication in the diabetic patients, it is still a matter of debate, because management of neuropathic pain which frequently does not respond to traditional analgesics, is a challenging task for physicians. Furthermore, due to their severe side effects, the use of traditional medications in improving the neuropathic pain, such as analgesics, anti-epileptics, and antidepressants, are particularly not convincing<sup>(10)</sup>. Additionally, these drugs can ameliorate the symptoms of the disease with no impact on the pathogenesis of the neuropathy<sup>(11, 12)</sup>. The potential pharmacotherapies that have emerged based on the pathophysiology of diabetic neuropathy include restoring anti-oxidant imbalance and reduction of inflammation and oxidative stress. As a result, there is an advance need for a safe and effective multi-targeted therapy to ameliorate the progression of diabetic neuropathy. As an herbal-based phytochemical compounds, polyphenols<sup>(13)</sup> possess pleiotropic activities predominantly anti-oxidants and anti-inflammatory effects. Thus, they might be used in the treatment of the variety illnesses such as diabetes and its complications<sup>(14)</sup>. Natural polyphenols have also recently been mentioned as potential neuroprotective medications for diabetes<sup>(15)</sup>. Based on the pathogenesis of diabetic neuropathy and the mechanisms that associated with polyphenol's prevention of the disease progression, the

introduction of polyphenols as a unique therapeutic agent in diabetic neuropathy came to the light<sup>(14)</sup>. Therefore, supplementation of polyphenol compounds along with conventional therapy is needed for patients to decrease the progression of diabetes and its complications<sup>(15)</sup>. Resveratrol is an herbal-based polyphenolic compound, it exerts many effects, mainly anti-inflammatory, anti-oxidant, and cytoprotective effects. These effects have been investigated mostly in preclinical studies<sup>(16)</sup>. Several clinical trials have demonstrated that resveratrol supplementation at different doses is safe and well tolerated.<sup>(17-19)</sup>

Furthermore, many studies evaluated the anti-diabetic effects of resveratrol, and they provided evidences on the potential mechanisms of resveratrol in insulin sensitizing activity, improvement of insulin resistance, restoring abnormal insulin level, blood glucose and insulin-like growth factors (IGFs) and enhancing glucose uptake and metabolism<sup>(20-22)</sup>. Additionally, in a randomized controlled clinical trial, resveratrol supplementation improved pain and the aspects of well-being and QoL in postmenopausal women<sup>(23)</sup>. Therefore, based on the aforementioned effects of resveratrol, we hypothesized that resveratrol supplementation in patient with diabetic neuropathy is important in restoring abnormal metabolic function and improving QoL via managing diabetic neuropathic pain. For this purpose, the current study aimed to assess the role of resveratrol in the improvement of the QoL of diabetic patients with neuropathic complication at the Sulaimani Diabetes and Endocrinology center which is a public center belong to Sulaimani Directorate of Health-Ministry of Health-Kurdistan Region-Iraq.

## Methodology

### *The ethical concern*

The study was a double blind randomized interventional placebo-controlled clinical trial. The research proposal was verified by the Registration and Ethical Committee of the Pharmacy College, Sulaimani University, the registration number was PH30-21 in 14.11.2021. The protocol of the study was in compliance with the Declaration of Helsinki. Additionally, the study has been registered in Clinicaltrial.gov with identifier # NCT05172947(<https://clinicaltrials.gov/ct2/show/NCT05172947>). It has also approved by the Scientific Research Department-Sulaimani DOH with the number 14812 in 16.11.2021. All the patients were signed the informed consent before enrollment to the study and their participations were volunteer based. The eligible patients were included in the study and they were randomly allocated into two groups.

**Inclusion and Exclusion criteria****Inclusion criteria**

The patients were eligible for the study if their age was between 50-65 years old of either sex and had type two diabetes mellitus (T2DM). Other inclusion criteria were; the duration of the disease  $\geq 5$  years, a glycosylated hemoglobin (HbA1c) of greater than 7% with diabetic neuropathy whether on oral hypoglycemic agents or insulin or their combination. The diagnosis was confirmed by a senior clinical endocrinologist and clinical neurologist with a score of  $\geq 4$  on the Michigan Neuropathy Screening Instrument (MNSI) <sup>(24)</sup>, and who had a pain score of  $\geq 4$  on daily basis that measured on a pain rating scaled in 0-10 grades. The pain has to be presented for approximately six months.

**Exclusion criteria**

The renal transplanted patients or on renal dialysis, older age with cardiovascular or hepatic diseases, pregnant or breastfeeding were excluded. Furthermore, heavy alcohol drinkers, or any psychiatric disorder were also not included. Other exclusion criteria were related to the patients' health status and medications history such as having pernicious anemia and hypothyroidism that could be a source for neuropathy, patients with past history of allergy to the medications, or on pentoxifylline and antioxidants three months prior the enrollment were also excluded.

**Study protocol, Recruitment, Grouping and Treatment**

A total of seventy-six patients with peripheral diabetic neuropathy who attended the Center for Diabetes and Endocrinology, Directorate of Health/Sulaimani City, were screened for eligibility.

The eligible patients (n=61) were randomized to 1:1 ratio and divided into two groups. First group (n=31); patients received resveratrol 500 mg capsule orally once daily in the morning after meal (Trans-Resveratrol natural pure powder  $\geq 98\%$  from Apollo Healthcare Resources, Singapore), with their conventional hypoglycemic medications for 3 months. The conventional hypoglycemic medications used by the patients in both groups were metformin, glimepiride and/or insulin with sitagliptin, few patients were had sodium-glucose cotransporter 2 inhibitors such as dapagliflozin or empagliflozin in both groups. Second group (n=30); patients received placebo (Carboxy Methyl Cellulose formulated similar in shape and color to the resveratrol capsule) with conventional hypoglycemic drugs. The study was conducted as a three-month follow-up with four visits; at baseline, month 1, month 2, and month 3 of the study and the interval between each visit was four weeks (Figure 1). The duration of study was ten months, it started on December 2021 till September 2022. The

purpose, main side effects, and benefits of the study were clarified to all the patients prior the enrollment into the trial.

**Outcome measures**

The primary outcome measures in the present study were the assessment of the glycemic status via evaluating the mean change in fasting blood glucose and QoL using the validated English version of RAND 36-Item Health Survey version-1 questionnaire every month for three months. The questionnaire was filled in by the researchers <sup>(25)</sup>. Lipid profiles of all the participants also have been measured in the baseline and after three months (pre- and post-interventions) as a secondary outcome measure. The study was conducted as a multidisciplinary team work. A Senior clinical endocrinologist, a clinical neurologist and a clinical pharmacist were involved in the study. They were involved in the diagnosis, assessment of the QoL and follow-up of the patients.

**Assessment of the Quality of life (QoL)**

The impact of resveratrol on improving the glycemic status and QoL of diabetic patients with neuropathic complications were assessed by using a validated RAND-36-Item Health Survey version-1 questionnaire. RAND 36 assesses eight health concepts during the study period with multiple item scales (35 items): 10 items for physical functioning, 4 for role limitation due to physical problems, 3 for role limitations due to emotional problems, 2 for social functioning, 5 for emotional-well-being, 4 for vitality (energy/fatigue), 2 for pain, and 5 for general health perceptions. Furthermore, one item reflects the change in perceived health within the last twelve months. All questions in RAND 36 have a score from 0 to 100, with 100 indicates the highest level of functioning which reflect better health or functioning <sup>(25)</sup>. Out of the eight domains four are associated with the physical health (physical functioning, physical health limitation, pain and general health) and four linked to mental health (social functioning, emotional wellbeing, fatigue and emotional problem limitation). In the current study, RAND 36 health survey questionnaire was self-administered at baseline and continued every month until the study was completed.

**Assessment of lipid profile**

In this study, the effect of resveratrol supplementation on the lipid profile (serum cholesterol, triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) of the patients were investigated twice; at the baseline and at day 90 using SIEMENS- Dimension, Germany kits.

**Statistical analysis**

Data of this study were analyzed using GraphPad Prism (GraphPad version 9.4.1 software LLC, 2022). The Shapiro-Wilk test was used to examine the normal distribution of the variables.

The continuous data was expressed as means  $\pm$  standard deviation (SD). The continuous variable in analysis of RAND-36 subscales to determine the differences between resveratrol and placebo group in the different time point (baseline, month 1, month 2, month 3) was analyzed utilizing Two-Way ANOVA, repeated measure test confirmed by Benferroni multiple comparison. Categorical data were expressed as a number and percentage and Fisher's exact test was used to determine the difference between the two groups. Continuous demographic variable was analyzed by using un-

paired t-test for comparison between the groups. A P value  $<0.05$  considered as statistically significant.

**Results**

A total of 76 patients were screened for eligibility, and 15 failed to meet inclusion criteria. The remaining 61 patients were randomized to receive resveratrol 500mg capsule (n=31) and placebo group (n=30), From each group 25 patient completed the study (Figure 1). The basic characteristics of the participants is summarized in table 1.

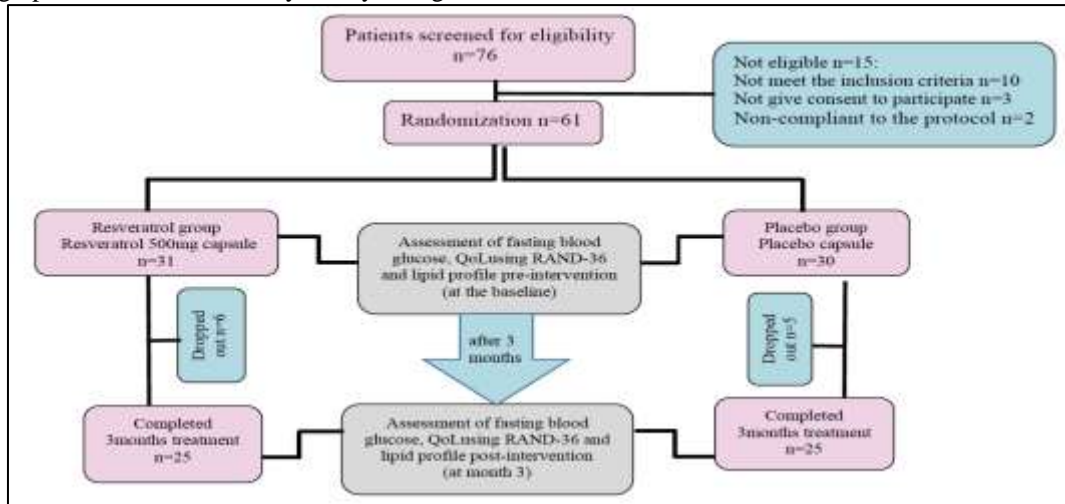


Figure 1. Flowchart of the study design.

\*QoL; Quality of life, RAND-36; RAND-36-Item Health Survey version-1 questionnaire, n=number of the patients.

Table 1. Characteristics of resveratrol and placebo treated patients at the baseline

Variables	Resveratrol n=25	Placebo n=25	P-value
Male	11(44%)	10(40%)	0.998
Female	14(56%)	15(60%)	
Age mean $\pm$ SD (years)	61.64 $\pm$ 8.577	60 $\pm$ 7.192	0.479
Duration of Diabetes (years)	15.8 $\pm$ 4.848	16.3 $\pm$ 3.913	0.678
Body weight (Kg)	75 $\pm$ 13.33	72 $\pm$ 10.83	0.329
Surgical History (Yes)	12(48%)	13(56.5%)	0.999
Alcohol consumption (No)	100%	100%	ns
Smoking (Yes)	1(4%)	1(4.35%)	ns

\*Data expressed as number and percentage, mean $\pm$  Standard deviation (SD). Fisher's exact test and unpaired t-test were used to determine the differences between the two groups for both categorical and continuous variables respectively. ns; non-significant.

The fasting blood glucose in both groups were analyzed in the baseline and at the end of the study. In resveratrol and in placebo groups, the FBG level was found to be 224.24 $\pm$ 81.67 and 224.20 $\pm$ 88.76 respectively in both groups at the

baseline, and the levels became 163.12 $\pm$ 42.92 and 251.920 $\pm$ 98.242 respectively at the third months. This result displayed a significant improvement (p<0.05) in FBG level in treated group (Table 2).

Table 2. Mean differences of Fasting Blood Glucose in patients with diabetic neuropathy.

Time	Resveratrol n=25	Placebo n=25	Mean Difference	P-value
Baseline	224.24 $\pm$ 81.67	224.20 $\pm$ 88.76	0.04	0.9987
Last day of month 3	163.12 $\pm$ 42.92 <sup>a</sup>	251.920 $\pm$ 98.242 <sup>b</sup>	-88.8	0.0001

\*Values are expressed as Mean±SD. SD; standard deviation. *n*: number of patients. Data analyzed by independent t-test. \* Indicate significant difference with the baseline. non-identical superscript letters (a,b) indicates statistical difference between the different groups. *P-value* <0.05 is consider as statistically significant.

The comparison of the all domains of RAND 36 between the two groups is shown in figure 2,3,4,5,6. The Medical Outcomes Study Short Form-36 component analysis demonstrated two dissimilar concepts measured by the RAND-36: a physical dimension, and a mental dimension (26). The results showed that resveratrol group exhibited a significant

increase (*p*<0.05) in almost all domains in comparison with placebo group (Figure 2,3,4,5,6). The improvement in physical functioning, physical health, pain intensity, energy/fatigue, social functioning and emotional well-being were started mainly from month two and continued till the end of the study.

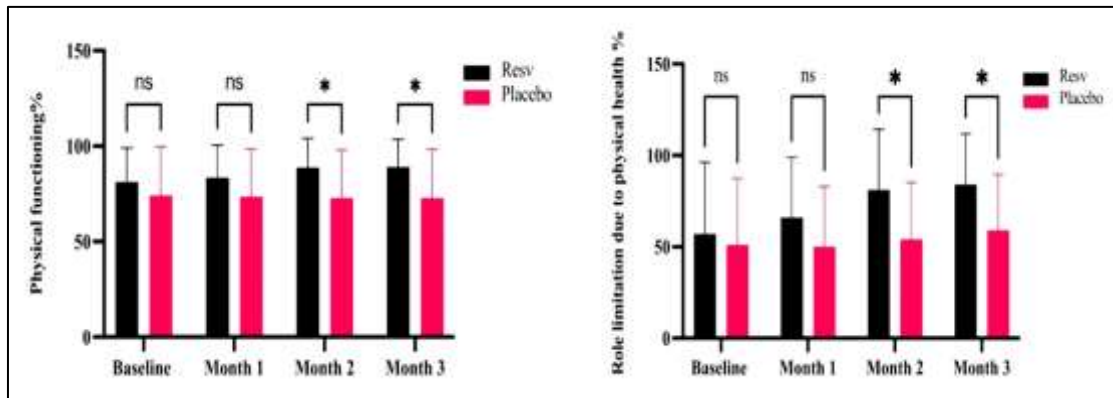


Figure 2. Effect of resveratrol on QoL scores-physical dimension (Physical functioning and Role limitation due to physical health).

\*Values are expressed as Mean±SD. Two-Way ANOVA, repeated measure test was used and confirmed by Benferroni’s multiple comparison test. ns; denotes non-significant. \**P-value* <0.05 is consider as statistically significant.

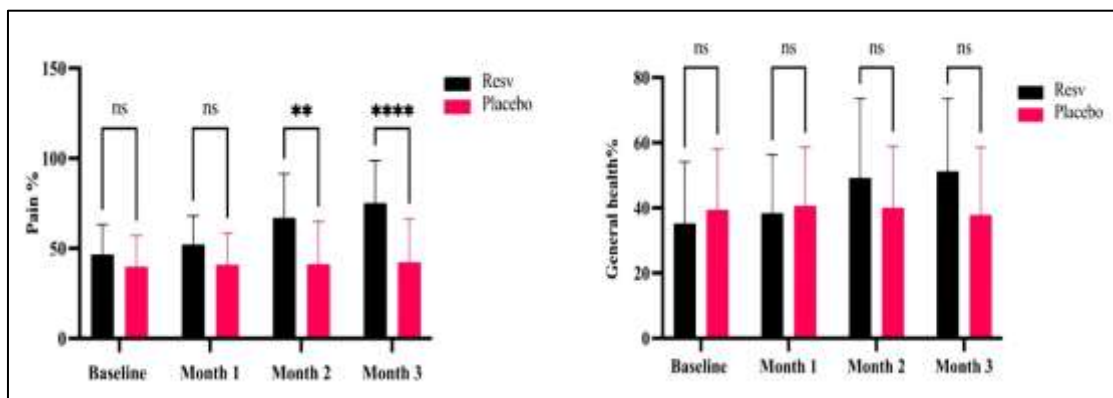


Figure 3. Effect of resveratrol on QoL scores-physical dimension (Pain, General health). Values are expressed as Mean±SD. Two-Way ANOVA, repeated measure test was used and confirmed by Benferroni’s multiple comparison test. ns; denotes non-significant. \**P-value* <0.05 is consider as statistically significant.



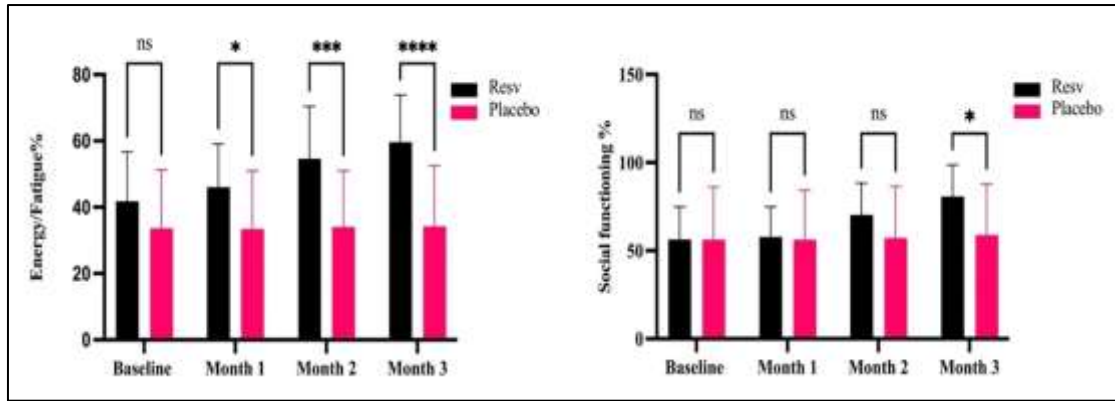


Figure 4. Effect of resveratrol on QoL scores-mental dimension (Energy/Fatigue, Social functioning). \*Values are expressed as Mean±SD. Two-Way ANOVA, repeated measure test was used and confirmed by Benferroni’s multiple comparison test. ns; denotes non-significant. \*P-value <0.05 is consider as statistically significant.

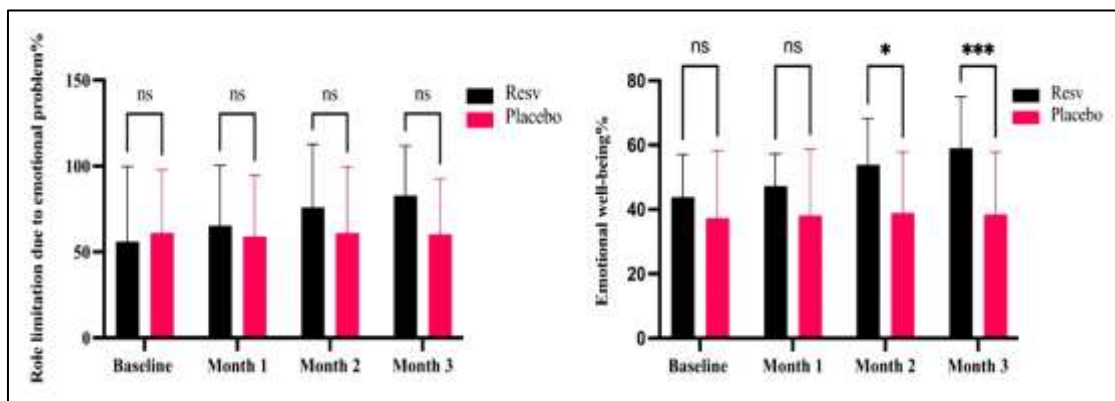


Figure 5. Effect of resveratrol on QoL scores-mental dimension (Role limitation due to emotional problem, Emotional well-deing). \*Values are expressed as Mean±SD. Two-Way ANOVA, repeated measure test was used and confirmed by Benferroni’s multiple comparison test. ns; denotes non-significant. \*P-value <0.05 is consider as statistically significant.

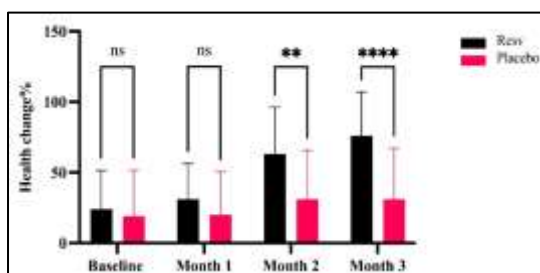


Figure 6. Effect of resveratrol on the health change subscale of RAND 36 health related QoL scores. \*values are expressed as Mean±SD. Two-Way ANOVA, repeated measure test was used and confirmed by Benferroni’s multiple comparison test. ns denotes non-significant. \*P-value <0.05 is consider as statistically significant.

The effect of resveratrol supplementation on the lipid profile (serum cholesterol, TG, LDL, HDL, VLDL) of the patients were also investigated, a non-significant difference (p>0.05) has been noticed between resveratrol group and the placebo one at the baseline and even after month 3 as well as within the same group no significant difference has been noted (Table 3).

**Table 3. The lipid profile of the patients after three months of resveratrol supplementation**

Lipid Profile (mmol/L)	Resveratrol n=25		Placebo n=25	
	0-Day	90-Day	0-Day	90-Day
S. Cholesterol	4.16±0.965	4.275±1.325	4.383±1.240	4.213±1.071
S.TG	1.727±0.992	1.624±1.094	1.917±0.758	2.061±0.948
S.LDL	2.684±0.962	2.786±1.063	2.892±1.038	2.780±0.883
S.HDL	1.003±0.183	1.172±0.347	1.022±0.433	0.970±0.433
S. VLDL	0.348±0.195	0.318±0.223	0.384±0.155	0.413±0.187

\*Values are expressed as Mean±SD. SD; standard deviation. *n*: number of patients. Two-Way ANOVA, repeated measure test was used and confirmed by Benferroni's multiple comparison test. S.TG; serum triglyceride, S.LDL; serum low density lipoprotein, S.HDL; serum high density lipoprotein, S. VLDL; serum very low-density lipoprotein.

## Discussion

It is obvious that diabetic peripheral neuropathy exerts a marked decline in the QoL of diabetic patients<sup>(27)</sup>. The pain that is accompanied this diabetic complication is adversely affecting the QoL of type 2 diabetic patients in terms of social functioning and psychological wellbeing and physical health<sup>(28)</sup>. Therefore, pain is counted as the most psychologically crippling symptoms of diabetic neuropathy<sup>(29)</sup>. Nearly 20% of the diabetic peripheral neuropathy patients experience neuropathic pain, which suggests a severe decline in QoL and functional ability<sup>(30)</sup>.

Previous research had already linked diabetic peripheral neuropathy to a significant decline in both physical and mental domains of QoL scores. Even in less severe cases, it has been found that the presence of diabetic neuropathy would be linked to significant declines in the physical domains of the RAND 36 scales<sup>(31)</sup>. The supplementation of 500mg resveratrol for three months in the current study was found to be associated with dramatic reduction in glucose level and an overall improvement in patient's QoL. There was improvement in patient's intensity of pain as shown in bodily pain score of the RAND 36 scale. The dramatic effect of resveratrol in amelioration of severity of pain in this study started after one month of the treatment and the effect became more obvious at the end of the study. It has been demonstrated that resveratrol has a pain controlling and anti-inflammatory effects in many pre-clinical and clinical studies<sup>(32,33,23,34)</sup>. The suggested mechanism of resveratrol in amelioration of pain was elucidated by reduction in the production of prostaglandins from arachidonic acid as a result of potential inhibition of cyclooxygenase -2 (COX-2) isoform, an enzyme that is in charge of inflammation and pain<sup>(35,36)</sup>. Furthermore, in animal model with chronic constriction injury, resveratrol was observed to reduce neuropathic pain after sciatic nerve injury and it lessen the mechanical allodynia and thermal hyperalgesic sensation, the suggested mechanism was through increases interleukin-4 (IL-4) receptor-mediated anti-inflammatory actions<sup>(37)</sup>. All these aforementioned mechanisms might be related to the

reduced physical pain in the participants in the current study.

Additionally, this work clarified that the use of resveratrol led to a significant improvement in physical functioning, physical health, social functioning, mental health, vitality, pain and health change subscales of RAND 36. However, the improvement in emotional problems and general health perceptions was non-significant. The findings of the present study can be supported by many previous pre-clinical studies in which resveratrol exhibited anti-anxiety, antidepressant activity and neuroprotection in different animal models and cell lines<sup>(38,39)</sup>. Moreover above, resveratrol has effects on multi-cerebral and neural signaling pathways so it has a remarkable role in amelioration of depressive status through various mechanisms including significant elevation in the level of dopamine, neuropeptide Y in the brain and in the frontal cortex it increases serotonin level<sup>(39)</sup>. Furthermore, the neuroprotective impact of resveratrol in diabetic peripheral neuropathy is likely caused by the fact that it modulates nuclear factor- $\kappa$ B (NF- $\kappa$ B) by enhancing nuclear erythroid 2-related factor 2 (Nrf2) activation and the production of anti-oxidative enzymes and consequently protecting peripheral nerves from apoptosis<sup>(40)</sup>.

On the other hand, the lipid profile of all the patients in this study have been observed in day one and in day 90 of the study because hyperlipidemia is considering as a risk factor for diabetic neuropathy<sup>(41)</sup>. There were non-significant changes in the components of the lipid profile. This outcome is inconsistent with the finding of the other clinical trial, where adjuvant use of resveratrol remarkably lowered the total cholesterol and TG levels in dyslipidemic subjects<sup>(42)</sup>. In the most recent dose-response meta-analysis of the randomized controlled trials, the add-on efficacy of resveratrol on blood lipid profile displayed significant reduction of LDL in the trials with a duration of more than three months and in patients with T2DM. This finding concluded that resveratrol may be of value in reducing TC, TG, and LDL-C levels in the blood and the dose of resveratrol intervention was an essential factor that affected the

level of LDL-C<sup>(43)</sup>. Therefore, the neutral effect of resveratrol supplement on these components of the lipid profile in the current trial might be related to the low dose and short duration of the treatment. After all, the current study has several limitations related to the limited number of the participants and the short period of the therapy (3 months). Use of low dose of resveratrol against its high dose was not investigated which is counted as another limitation of the study. On the contrary, the strength side of the work is that it was a double-blind randomized placebo controlled clinical trial which investigated the effect of resveratrol on the glycemic status and provided a convincing data for adjuvant use of resveratrol in the management of diabetic patients for improvement of QoL of the patients suffering from diabetic complications.

## Conclusion

The study concluded that resveratrol has a positive effect on reducing pain associated with diabetic neuropathy and improving the QoL of the patients with this complication. This could be related to the dramatic reduction in the glycemic status and amelioration of severity of pain by resveratrol. While resveratrol has a neutral effect on the components of the lipid profile in the current trial.

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The authors have not received any financial support for this work.

## Ethics Statements

The protocol of this work was registered and approved by the Ethical Committee of the College of Pharmacy, University of Sulaimani the registration number was PH30-21 in 14.11.2021. Additionally, the study has been registered in Clinicaltrial.gov with identifier # NCT05172947 (<https://clinicaltrials.gov/ct2/show/NCT05172947>). It has also approved by the Scientific Research Department-Sulaimani DOH with the number 14812 in 16.11.2021.

## Conflict of interest

The authors declared no conflicts of interest.

## Author contributions

G.S.M.A. contributed in the patient's screening, recruitment, data collection, assessment, analysis and reviewed the manuscript. B.H.M conceptualized the research design, analyzed the

data, wrote the first draft of the manuscript and completed the final version. H.S.N. as a clinical neurologist involved in the diagnosis of the cases and involved in patient screening and recruitments, reviewed the manuscript. All the authors reviewed and approved the final draft.

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