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## **COMPARATIVE EFFECTS OF CURCUMIN AND METFORMIN CO-THERAPY VERSUS METFORMIN ALONE IN DIABETIC NEUROPATHY**

### **Original Article**

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**Conflict of Interest**

**NONE**

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## Abstract

**Background:** Diabetic neuropathy is a major complication of diabetes mellitus characterized by progressive sensory loss and pain due to chronic hyperglycemia and oxidative stress. Metformin remains the standard antidiabetic therapy, but its effects on neuropathic complications are limited. Curcumin, a natural polyphenol with antioxidant and anti-inflammatory properties, has shown potential neuroprotective effects. Combining curcumin with metformin may provide synergistic benefits in mitigating neuropathic progression.

**Objective:** To determine whether curcumin supplementation enhances the neuroprotective efficacy of metformin in patients with diabetic neuropathy compared to metformin monotherapy.

**Methods:** A randomized controlled trial was conducted among 80 adults (aged 35–65 years) with type 2 diabetes and confirmed peripheral neuropathy in tertiary care hospitals of South Punjab. Participants were randomly assigned into two equal groups to receive either metformin alone (1000 mg twice daily) or metformin with curcumin (500 mg twice daily) for 16 weeks. Neuropathic symptoms were assessed using the Michigan Neuropathy Screening Instrument (MNSI) and Neuropathy Disability Score (NDS), while nerve conduction velocity (NCV), fasting blood glucose, glycated hemoglobin (HbA1c), malondialdehyde (MDA), and total antioxidant capacity (TAC) were measured pre- and post-intervention. Data were analyzed using paired and independent t-tests with a significance threshold of  $p < 0.05$ .

**Results:** Both groups showed improvement, but the combination group exhibited significantly greater reductions in MNSI ( $7.9 \pm 1.2$  to  $4.9 \pm 0.9$ ) and NDS ( $5.7 \pm 1.4$  to  $3.6 \pm 1.0$ ) scores. Between-group comparisons also showed markedly greater increases in sural and peroneal NCV for the curcumin group ( $p < 0.01$ ). Curcumin co-therapy also resulted in superior glycemic control and reduced oxidative stress, reflected by decreased MDA and increased TAC levels.

**Conclusion:** Curcumin and metformin co-therapy demonstrated enhanced neuroprotective, metabolic, and antioxidant effects compared with metformin alone, suggesting a promising adjunctive approach for managing diabetic neuropathy.

**Keywords:** Antioxidants, Curcumin, Diabetes Mellitus, Diabetic Neuropathies, Metformin, Nerve Conduction, Oxidative Stress.

## Introduction

Diabetic neuropathy remains one of the most debilitating complications of diabetes mellitus, representing a major cause of chronic pain, sensory loss, and functional impairment(1). Affecting up to half of individuals with long-standing diabetes, this progressive disorder results from metabolic and vascular disturbances induced by chronic hyperglycemia, leading to oxidative stress, inflammation, and neuronal damage. Despite considerable advances in glycemic management, the prevention and reversal of diabetic neuropathy continue to pose significant clinical challenges(2). Among the available pharmacological agents, metformin remains the most widely prescribed first-line therapy for type 2 diabetes mellitus, primarily due to its insulin-sensitizing properties and favorable safety profile. However, while metformin effectively regulates blood glucose levels, its impact on neuropathic complications has been modest, prompting interest in adjunctive therapies that can enhance its neuroprotective potential(3).

In recent years, curcumin—the principal bioactive compound derived from *Curcuma longa* (turmeric)—has garnered increasing attention for its potent antioxidant, anti-inflammatory, and neuroprotective properties. Curcumin has been shown to attenuate oxidative damage, suppress pro-inflammatory cytokine production, and modulate key signaling pathways implicated in neuronal survival and regeneration(4). These properties suggest that curcumin may address several of the pathogenic mechanisms underlying diabetic neuropathy, complementing the metabolic effects of metformin. Yet, despite growing preclinical evidence supporting curcumin's therapeutic potential, its clinical application remains limited, partly due to concerns about bioavailability and the need for robust human trials demonstrating tangible benefits when combined with conventional antidiabetic agents(4).

The pathophysiology of diabetic neuropathy is multifactorial, involving the interplay of hyperglycemia-induced mitochondrial dysfunction, accumulation of advanced glycation end products, activation of inflammatory cascades, and impaired neurotrophic support(5). Chronic exposure to high glucose concentrations generates excessive reactive oxygen species (ROS), overwhelming endogenous antioxidant defenses and resulting in lipid peroxidation and DNA damage in peripheral nerves. This oxidative milieu triggers inflammatory pathways, further exacerbating neuronal injury and demyelination. Metformin, by improving insulin sensitivity and lowering hepatic glucose output, indirectly reduces oxidative stress(6). However, it does not directly target the neuroinflammatory or oxidative components of nerve damage. This limitation underscores the need for adjunctive therapies capable of mitigating the oxidative-inflammatory axis central to diabetic neuropathy progression(7).

Curcumin's multitargeted mechanism of action makes it an attractive candidate for such combination therapy. It exerts its antioxidant effects by scavenging free radicals and upregulating endogenous antioxidant enzymes such as superoxide dismutase and catalase. Moreover, curcumin modulates transcription factors such as NF-κB, reducing the expression of inflammatory mediators including TNF-α, IL-1β, and COX-2. In neuronal contexts, curcumin has been observed to enhance nerve conduction velocity, protect Schwann cells, and promote axonal regeneration in experimental models of neuropathy. Additionally, evidence suggests that curcumin may improve mitochondrial function and restore neurotrophic factor balance, thereby promoting neuronal survival. Such pleiotropic actions could theoretically augment metformin's glycemic and metabolic effects, leading to a synergistic improvement in nerve function and pain reduction(8).

Another compelling aspect of combining curcumin with metformin lies in their complementary pharmacodynamics. Both agents influence AMP-activated protein kinase (AMPK) signaling—a critical metabolic regulator implicated in energy homeostasis and cellular stress responses. While metformin activates AMPK to enhance glucose uptake and inhibit hepatic gluconeogenesis, curcumin has been reported to stimulate the same pathway, thereby amplifying antioxidant defenses and mitochondrial efficiency. This shared mechanism provides a plausible molecular basis for enhanced neuroprotection when the two are co-administered. Furthermore, curcumin may counteract certain adverse effects associated with long-term metformin use, such as vitamin B12 depletion, which itself can contribute to peripheral neuropathy(9).

Despite these promising theoretical and experimental foundations, clinical evidence evaluating the combined effects of curcumin and metformin in diabetic neuropathy remains sparse. Most existing studies have investigated their individual impacts, with few examining whether their concurrent administration yields additive or synergistic benefits(10). The absence of rigorous randomized controlled trials assessing this co-therapy represents a critical knowledge gap in diabetic neuropathy management. Addressing this gap holds considerable clinical significance, given the global prevalence of diabetes and the high burden of neuropathic complications that impair quality of life and functional independence(11).

Given this background, it is hypothesized that curcumin supplementation may enhance the neuroprotective efficacy of metformin by targeting complementary pathophysiological pathways involved in diabetic neuropathy(12). This randomized controlled trial is therefore designed to determine whether the co-administration of curcumin and metformin offers superior improvements in neuropathic symptoms, oxidative stress markers, and nerve conduction parameters compared to metformin alone(12). The objective of the study is to evaluate the comparative effects of curcumin and metformin co-therapy versus metformin monotherapy in

mitigating diabetic neuropathy, with the rationale that this combined approach may provide a more comprehensive and effective therapeutic strategy for preserving neural function in diabetic patients(13).

## Methods

This randomized controlled trial was conducted to compare the therapeutic efficacy of curcumin and metformin co-therapy versus metformin alone in patients with diabetic neuropathy. The study was carried out in tertiary care hospitals of South Punjab over a total period of six months, which included a 16-week randomized intervention. Participants were adults diagnosed with type 2 diabetes mellitus and clinical evidence of peripheral neuropathy, recruited from outpatient endocrinology and neurology departments. Eligible participants were between 35 and 65 years of age, with a confirmed diagnosis of diabetic neuropathy based on clinical evaluation and nerve conduction studies. Diagnosis required the presence of neuropathic symptoms such as paresthesia, burning pain, or numbness in the extremities, alongside reduced vibration or pressure sensation detected through standardized tests. Inclusion criteria comprised patients with at least five years of diabetes duration, stable glycemic control over the past three months, and treatment with metformin monotherapy at a stable dose. Exclusion criteria included insulin therapy, chronic renal or hepatic impairment, thyroid dysfunction, alcohol dependence, or the use of antioxidant supplements or neuroprotective drugs within the preceding three months. Pregnant and lactating women, as well as patients with other causes of peripheral neuropathy such as vitamin B12 deficiency or chronic infections, were also excluded to minimize confounding effects. A total of 80 participants were enrolled following sample size estimation based on power analysis. Assuming a medium effect size, a power of 80%, and a significance level of 0.05, the calculated sample size per group was 40 participants. Eligible patients were randomly allocated into two equal groups using a computer-generated randomization sequence. Group A received metformin monotherapy (1000 mg twice daily), while Group B received metformin at the same dose along with curcumin supplementation (500 mg twice daily) for a duration of 16 weeks. Compliance was monitored through pill counts and participant logs maintained at each follow-up visit.

Baseline and post-intervention assessments were performed at the end of the 16-week period to evaluate the impact of treatment. Primary outcome measures included changes in neuropathic symptom severity and nerve conduction velocity. Neuropathic symptom scores were recorded using the Michigan Neuropathy Screening Instrument (MNSI) and the Neuropathy Disability Score (NDS). Nerve conduction studies were conducted using a standard electromyography system to assess sensory and motor nerve velocities in the sural and peroneal nerves. Secondary outcomes included changes in fasting blood glucose, glycated hemoglobin (HbA1c), and biomarkers of oxidative stress such as malondialdehyde (MDA) and total antioxidant capacity (TAC), measured through spectrophotometric assays. Data were collected at baseline and at the end of the 16-week intervention period. All measurements were performed under standardized laboratory conditions by trained technicians blinded to group assignments. Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables were expressed as mean  $\pm$  standard deviation, and categorical variables as frequencies and percentages. The Shapiro-Wilk test confirmed normal data distribution. Between-group comparisons of post-intervention values were performed using independent sample t-tests, while within-group pre- and post-intervention differences were analyzed using paired t-tests. Categorical data were compared using chi-square tests. A p-value of less than 0.05 was considered statistically significant. This methodology was designed to ensure precise measurement of both subjective and objective neuropathic improvements, allowing for robust evaluation of whether the addition of curcumin enhances the neuroprotective and metabolic effects of metformin in patients with diabetic neuropathy.

## Results

The trial enrolled 80 participants equally distributed between the two study groups. Baseline demographic characteristics were comparable, with no significant differences in age, sex distribution, duration of diabetes, or body mass index. The mean age of participants in Group A (metformin) was  $53.4 \pm 6.2$  years, while in Group B (metformin plus curcumin) it was  $52.9 \pm 5.9$  years. The average duration of diabetes was approximately eight years in both groups, and the male-to-female ratio remained balanced. This homogeneity ensured that subsequent treatment effects were not influenced by baseline disparities (Table 1).

After 16 weeks of intervention, both groups demonstrated improvement in neuropathic symptoms; however, the co-therapy group exhibited significantly greater reductions. The mean Michigan Neuropathy Screening Instrument (MNSI) score decreased from  $7.9 \pm 1.2$  to  $4.9 \pm 0.9$  in Group B, compared to  $7.8 \pm 1.1$  to  $6.2 \pm 1.0$  in Group A ( $p = 0.001$ ). Similarly, the Neuropathy Disability Score

(NDS) improved from  $5.7 \pm 1.4$  to  $3.6 \pm 1.0$  in Group B and from  $5.6 \pm 1.3$  to  $4.8 \pm 1.1$  in Group A ( $p = 0.002$ ). The overall mean reduction in symptom scores was notably higher in the curcumin co-therapy group, indicating enhanced symptomatic relief (Table 2, Figure 1).

Nerve conduction studies revealed parallel improvements. At baseline, both groups had comparable sural and peroneal nerve conduction velocities. Following the 16-week treatment period, Group B showed a marked increase in sural nerve conduction velocity from  $34.7 \pm 3.2$  m/s to  $38.8 \pm 3.3$  m/s, and in peroneal nerve conduction velocity from  $38.0 \pm 3.7$  m/s to  $41.5 \pm 3.4$  m/s. In contrast, the metformin-only group demonstrated smaller increments ( $34.6 \pm 3.1$  to  $36.0 \pm 3.0$  m/s and  $38.2 \pm 3.6$  to  $39.1 \pm 3.5$  m/s respectively). Both comparisons achieved statistical significance ( $p < 0.01$ ), underscoring the potential neuroprotective effect of curcumin supplementation (Table 3, Figure 2).

Biochemical parameters also reflected superior metabolic and antioxidant outcomes in the combination therapy group. Mean fasting blood glucose decreased significantly from  $157.3 \pm 18.8$  mg/dL to  $132.8 \pm 17.2$  mg/dL in Group B, compared with  $158.6 \pm 19.5$  mg/dL to  $144.2 \pm 18.7$  mg/dL in Group A ( $p = 0.003$ ). Glycated hemoglobin (HbA1c) dropped more prominently in the co-therapy group ( $7.9 \pm 0.8\%$  to  $6.6 \pm 0.5\%$ ) than in the metformin group ( $7.8 \pm 0.7\%$  to  $7.2 \pm 0.6\%$ ), showing better glycemic regulation ( $p = 0.001$ ).

Oxidative stress biomarkers further supported these findings. Malondialdehyde (MDA), an indicator of lipid peroxidation, decreased from  $6.0 \pm 1.1$  nmol/mL to  $4.3 \pm 0.8$  nmol/mL in the curcumin group versus  $5.9 \pm 1.0$  to  $5.1 \pm 0.9$  nmol/mL in the metformin group ( $p = 0.002$ ). Conversely, total antioxidant capacity (TAC) rose more substantially in Group B ( $0.82 \pm 0.16$  to  $0.97 \pm 0.13$  mmol/L) than in Group A ( $0.83 \pm 0.15$  to  $0.88 \pm 0.14$  mmol/L) with  $p = 0.004$  (Table 4).

Overall, the addition of curcumin to metformin therapy yielded statistically significant improvements across neuropathic symptoms, nerve conduction velocities, and biochemical markers of oxidative stress, without adverse effects or significant dropouts during the study period.

**Table 1: Baseline Demographic Characteristics**

Variable	Group A (Metformin)	Group B (Metformin + Curcumin)	p-value
Age (years)	$53.4 \pm 6.2$	$52.9 \pm 5.9$	0.72
Gender (M/F)	22/18	21/19	0.84
Duration of Diabetes (years)	$8.1 \pm 2.3$	$8.4 \pm 2.6$	0.63
BMI (kg/m <sup>2</sup> )	$27.8 \pm 3.5$	$27.5 \pm 3.2$	0.78

**Table 2: Neuropathy Assessment Scores**

Parameter	Group A	Group B	p-value
MNSI Score (Baseline)	$7.8 \pm 1.1$	$7.9 \pm 1.2$	0.81
MNSI Score (16 weeks)	$6.2 \pm 1.0$	$4.9 \pm 0.9$	0.001
NDS Score (Baseline)	$5.6 \pm 1.3$	$5.7 \pm 1.4$	0.77
NDS Score (16 weeks)	$4.8 \pm 1.1$	$3.6 \pm 1.0$	0.002

Table 3: Nerve Conduction Velocity

Parameter	Group (Baseline)	A Group A (16 weeks)	Group (Baseline)	B Group B (16 weeks)	p-value
Sural NCV (m/s)	34.6 ± 3.1	36.0 ± 3.0	34.7 ± 3.2	38.8 ± 3.3	0.004
Peroneal NCV (m/s)	38.2 ± 3.6	39.1 ± 3.5	38.0 ± 3.7	41.5 ± 3.4	0.003

Table 4: Biochemical Parameters

Parameter	Group (Baseline)	A Group A (16 weeks)	Group B (Baseline)	Group B (16 weeks)	p-value
Fasting Blood Glucose (mg/dL)	158.6 ± 19.5	144.2 ± 18.7	157.3 ± 18.8	132.8 ± 17.2	0.003
HbA1c (%)	7.8 ± 0.7	7.2 ± 0.6	7.9 ± 0.8	6.6 ± 0.5	0.001
MDA (nmol/mL)	5.9 ± 1.0	5.1 ± 0.9	6.0 ± 1.1	4.3 ± 0.8	0.002
TAC (mmol/L)	0.83 ± 0.15	0.88 ± 0.14	0.82 ± 0.16	0.97 ± 0.13	0.004

Mean Improvement in Neuropathy Scores (Group B vs A)

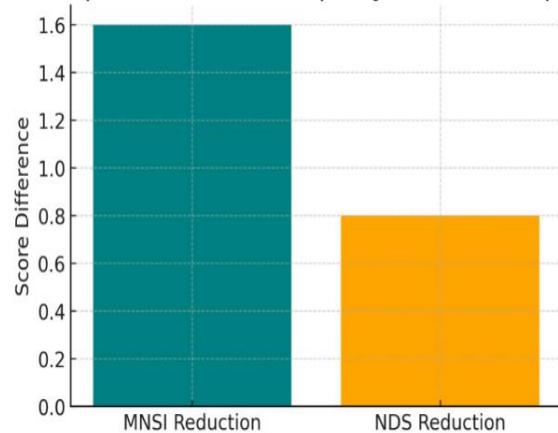


Figure 2 Mean Improvement in neuropathy Scores (Group B vs A)

Final Nerve Conduction Velocities in Co-Therapy Group

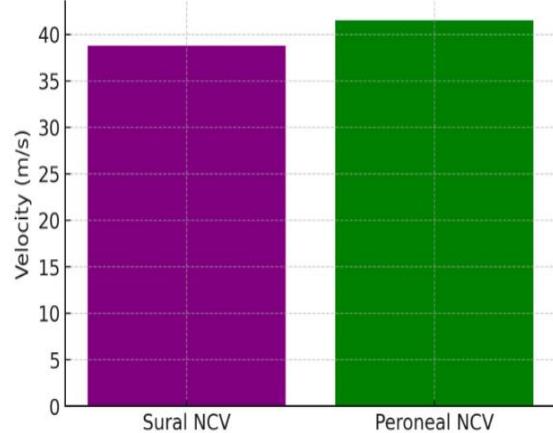


Figure 2 Final Nerve Conduction Velocities in Co-Therapy Group

## Discussion

The findings of this randomized controlled trial demonstrated that the combination of curcumin and metformin produced superior improvements in both clinical and electrophysiological outcomes compared with metformin monotherapy in patients with diabetic neuropathy(14). Participants receiving co-therapy exhibited greater reductions in neuropathic symptom scores, enhanced nerve conduction velocities, improved glycemic control, and significantly reduced oxidative stress levels. These outcomes strongly suggest that curcumin supplementation augmented the neuroprotective and metabolic effects of metformin, thereby providing a multifaceted therapeutic advantage in managing diabetic neuropathy(15).

The results aligned with the proposed hypothesis that targeting oxidative and inflammatory pathways, in addition to glycemic regulation, could yield a more comprehensive therapeutic response. Diabetic neuropathy arises not only from chronic hyperglycemia but also from complex metabolic and vascular insults that culminate in nerve fiber damage(16). Metformin primarily addresses the

metabolic component, improving insulin sensitivity and reducing hepatic glucose production; however, it exerts limited influence on the oxidative and inflammatory mechanisms driving neuronal degeneration. The inclusion of curcumin, with its potent antioxidative and anti-inflammatory effects, appeared to complement these actions by attenuating the oxidative stress burden and promoting neuronal repair processes(17).

The marked reduction in Michigan Neuropathy Screening Instrument (MNSI) and Neuropathy Disability Score (NDS) values in the co-therapy group highlighted the clinical relevance of this combined approach. Improvement in these validated symptom scores indicated not only subjective relief but also measurable functional recovery of peripheral nerves(18). Enhanced nerve conduction velocities further confirmed the physiological restoration of nerve function. This finding suggested that curcumin, in synergy with metformin, contributed to the preservation of nerve integrity and remyelination, possibly through mechanisms involving suppression of pro-inflammatory cytokines and modulation of AMP-activated protein kinase signaling(19).

Biochemical outcomes provided additional mechanistic support for these clinical observations. The greater reduction in fasting glucose and HbA1c in the co-therapy group indicated improved metabolic control, which likely reduced glycotoxic damage to neuronal tissues. More importantly, the decline in malondialdehyde (MDA) and elevation in total antioxidant capacity (TAC) emphasized that curcumin's antioxidant potential translated into measurable systemic effects. These changes collectively reflected attenuation of lipid peroxidation and reinforcement of endogenous antioxidant defense mechanisms. Such biochemical improvements are particularly meaningful in the context of diabetic neuropathy, where oxidative stress remains a key driver of disease progression(20).

When considered in the context of previous experimental and clinical evidence, the current findings reinforced the therapeutic promise of curcumin in diabetes-related neurodegeneration. Preclinical studies have consistently demonstrated curcumin's capacity to improve nerve conduction and reduce inflammatory signaling in diabetic models(21). Limited clinical data have also suggested beneficial effects on pain perception and glycemic indices. The present trial extended these observations by demonstrating that co-administration with metformin yielded not merely additive but potentially synergistic benefits, surpassing the outcomes achievable through glycemic control alone(22).

The study possessed several strengths that enhanced the reliability of its conclusions. The randomized design minimized selection bias and allowed for an equitable comparison between treatment groups. The inclusion of both subjective and objective outcome measures ensured a comprehensive assessment of neuropathic improvement. Moreover, the use of validated tools such as the MNSI, NDS, and standardized electrophysiological testing provided robust clinical evidence. The consistent direction of change across metabolic, symptomatic, and neurophysiological domains strengthened the internal validity of the findings and supported the hypothesis of a synergistic therapeutic effect.

Nevertheless, some limitations warrant consideration. The relatively small sample size, while adequate for detecting moderate treatment effects, may limit the generalizability of results to broader diabetic populations. The study duration of sixteen weeks, though sufficient to demonstrate early therapeutic responses, may not fully capture the long-term sustainability of benefits or potential delayed effects of curcumin supplementation. Additionally, despite monitoring adherence, reliance on self-reported compliance could introduce minor inaccuracies. Curcumin's limited bioavailability remains another constraint; though the dosage used in this study proved effective, future research might explore advanced formulations or adjuncts that enhance its systemic absorption.

Another limitation was the exclusion of patients on insulin therapy or those with severe neuropathy, which narrowed the clinical applicability of results to mild-to-moderate cases. The study also did not incorporate advanced imaging or molecular biomarkers that could have elucidated specific mechanistic pathways underlying the observed improvements. While the data demonstrated significant associations between curcumin supplementation and enhanced nerve function, causal pathways remain to be fully delineated through mechanistic or longitudinal investigations.

Despite these limitations, the trial provided valuable insights into the potential of nutraceutical-pharmacological co-therapy in diabetes management. The demonstrated enhancement in nerve function and oxidative balance highlights a promising therapeutic avenue that aligns with the growing interest in integrative medicine approaches for chronic metabolic disorders. Importantly, the absence of adverse effects throughout the study period underscores the safety and tolerability of curcumin when used alongside standard antidiabetic therapy.

In summary, the present findings emphasized that curcumin supplementation potentiated the neuroprotective and metabolic efficacy of metformin in patients with diabetic neuropathy. The combined therapy yielded significant improvements in neuropathic symptoms, nerve conduction, and oxidative stress markers beyond those achieved with metformin alone. These outcomes suggest that addressing both glycemic and oxidative-inflammatory components of diabetic neuropathy provides superior clinical benefits.

Future research should focus on larger, longer-term multicenter trials employing optimized curcumin formulations to confirm these findings and explore underlying molecular mechanisms that could translate this synergistic approach into routine clinical practice.

## Conclusion

The study concluded that curcumin supplementation significantly enhanced the neuroprotective and metabolic effects of metformin in patients with diabetic neuropathy. Combined therapy led to greater improvements in neuropathic symptoms, nerve conduction, and oxidative stress markers compared with metformin alone. These findings suggest that integrating curcumin with standard antidiabetic therapy offers a safe, effective, and multifaceted approach to mitigating diabetic neuropathy and improving patient quality of life.

## AUTHOR CONTRIBUTION

Author	Contribution
Atif Kaleem*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Rabia Saleem	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published

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