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Efficacy and Safety of Transdermal Medical Cannabis (THC:CBD:CBN formula) to Treat Painful Diabetic Peripheral Neuropathy of Lower Extremities

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Keywords
Transdermal medical cannabis · Painful · Diabetic peripheral neuropathy · Clinical trial

Abstract

Introduction: Diabetic peripheral neuropathy (DPN) represents a prevalent neurological complication affecting millions of patients globally. This clinical investigation evaluated the therapeutic efficacy and safety profile of a novel transdermal medical cannabis formulation (THC:CBD:CBN) in treating painful DPN of the lower extremities. ***Methods:*** This phase III, double-blind, placebo-controlled, randomized clinical trial was conducted at Don Chan Hospital, Thailand, enrolling 100 participants over a 12-week intervention period. Using a computer-generated randomization sequence, participants were allocated to receive either the standardized cannabis formulation or a matched placebo. The primary outcome measure comprised pain intensity assessment using the validated Thai version of the Neuropathic Pain Symptom Inventory (NPSI-T). Secondary outcomes encompassed treatment-emergent adverse events and dermatological manifestations. Statistical analyses were performed using SPSS Version 28.0, incorporating generalized estimating equation (GEE) modeling and Analysis of Covariance (ANCOVA). The study protocol received approval from the Institutional Review Board of Khon Kaen University and the Kalasin Provincial Public Health Office Ethics Committee, with trial registration in the Thai Clinical Trials Registry. ***Results:*** The intervention group demonstrated statistically significant reductions in NPSI-T scores across all measured dimensions ($p < 0.001$). Mean total NPSI-T scores decreased markedly from 25.60 to 5.57 in the treatment cohort, contrasting with minimal reduction from 25.24 to 22.85 in the placebo group. GEE analysis revealed significant pain amelioration at weeks 4, 8, and 12 ($p < 0.001$). The cannabis formulation exhibited an excellent safety profile, with only 10% of participants reporting mild adverse events,

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comparable to placebo group outcomes. ***Conclusion:*** This novel transdermal medical cannabis formulation (THC:CBD:CBN) demonstrated significant therapeutic efficacy in ameliorating painful DPN symptoms while maintaining a favorable safety profile. These findings provide robust clinical evidence supporting its potential as an innovative therapeutic option for managing painful DPN.

Introduction

Diabetic peripheral neuropathy (DPN) constitutes a major neurological complication of diabetes mellitus, affecting millions of patients worldwide. A comprehensive systematic review and meta-analysis conducted by Sun et al. [1] demonstrated that the global prevalence of DPN among patients with type 2 diabetes varies substantially, ranging from 20% to 78.8%, with a pooled prevalence of 31.5% (95% CI: 24.4–39.3) [1]. This marked variation in prevalence rates has been attributed to multiple factors, including diabetes duration, heterogeneity in diagnostic methodologies, and geographical disparities. Contemporary studies have documented distinct grades of severity: mild (17.3%), moderate (8.2%), and severe (1.1%) [2].

Epidemiological investigations have revealed significant regional variations, with European studies reporting DPN prevalence rates of 20–60%, while Asian studies indicate rates between 15 and 40% [1, 3]. Within Thailand, several investigations have documented DPN prevalence, with a multicenter study by Malik et al. [4] establishing rates of 28.1–34.0% among patients with type 2 diabetes [4–6]. These findings align with regional epidemiological patterns documented in the International Diabetes Federation Atlas [7]. Of particular significance, our study region demonstrated a notably higher DPN prevalence of 97.7% among diabetic patients [4, 8, 9], underscoring the substantial burden of this condition within this specific population.

The pathophysiology of DPN is characterized by acute and chronic pain manifestations, progressive sensory loss, and an elevated risk of foot ulceration and subsequent amputation. These clinical features primarily stem from persistent nerve inflammation and dysfunction precipitated by chronic hyperglycemia [10, 11].

Contemporary treatment approaches for painful DPN encompass preventive strategies, behavioral modifications, and pharmacological interventions. However, current therapeutic modalities frequently demonstrate limited efficacy, leaving a substantial proportion of patients with inadequate pain management [12, 13]. This significant therapeutic gap has catalyzed investigations into alternative treatment strategies, including medical cannabis, which has demonstrated promising results in the management of various chronic pain conditions [14–17].

Medical cannabis exerts its therapeutic effects primarily through modulation of the endocannabinoid system, specifically via interaction with peripheral CB1 and CB2 receptors. These receptor subtypes, which are abundantly expressed in peripheral nervous tissue and surrounding structures, serve crucial functions in nociceptive modulation and neuroprotection. Δ9-tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, demonstrates high binding affinity for both receptor subtypes [18]. The activation of CB1 receptors mediates antinociceptive effects through attenuation of pain signal transmission, while CB2 receptor stimulation confers anti-inflammatory and neuroprotective properties.

The therapeutic potential of cannabis-based medicines is further enhanced through the synergistic interaction between THC and other cannabinoids, notably cannabidiol (CBD) and cannabinol (CBN). This pharmacological synergy in cannabinoid receptor activation presents a promising mechanistic pathway for ameliorating neuropathic manifestations. Despite burgeoning clinical interest in cannabis-based therapeutic agents for pain management, a substantial knowledge gap persists regarding the therapeutic efficacy of specific cannabinoid combinations in treating DPN. This limitation underscores the critical need for rigorous, well-designed clinical trials to establish evidence-based treatment protocols [14, 17, 19–21].

Despite encouraging preclinical evidence suggesting the analgesic and neuroprotective properties of cannabinoids [22, 23], robust clinical validation remains insufficient. The intricate interactions between cannabinoid compounds and the endocannabinoid system in DPN pathophysiology have not been fully elucidated [24]. Furthermore, optimal cannabinoid ratios and delivery systems for DPN management remain largely unexplored [20]. The present investigation addresses these critical knowledge gaps, potentially establishing novel therapeutic approaches for DPN management.

Among the various routes of cannabinoid administration, transdermal delivery presents distinct advantages for DPN treatment. This application method potentially offers targeted therapeutic effects with minimized systemic adverse reactions compared to oral administration [25, 26]. Moreover, transdermal delivery systems demonstrate

the capacity to maintain more consistent plasma cannabinoid concentrations, potentially enhancing therapeutic outcomes [25, 27, 28].

The therapeutic efficacy of cannabis preparations is significantly influenced by their specific cannabinoid composition. Our investigation focuses on a naturally derived, full-spectrum, THC-predominant formulation with a precisely defined THC:CBD:CBN ratio. This specific composition was selected based on preclinical evidence suggesting enhanced dermal absorption [29] and superior efficacy in neuropathic pain management [30, 31]. Within this formulation, THC serves as the primary analgesic component, while CBD and CBN contribute complementary therapeutic effects, including anti-inflammatory properties and potential enhancement of THC-mediated analgesia [24, 32].

Preclinical investigations of this specific cannabis oil formulation have yielded promising results regarding absorption kinetics and therapeutic efficacy. In experimental models of neuropathic pain, transdermal administration of this THC:CBD:CBN combination demonstrated superior analgesic efficacy compared to single-cannabinoid preparations [33, 34]. Additionally, pharmacokinetic analyses revealed enhanced bioavailability [35, 36] and more sustained plasma cannabinoid concentrations compared to oral administration routes [37].

Notwithstanding the promising preclinical findings, there remains a significant paucity of robust clinical evidence supporting the therapeutic application of this specific cannabis formulation in DPN management. While preliminary small-scale investigations and observational reports suggest potential therapeutic benefits [23, 38, 39], well-designed randomized controlled trials are imperative to establish comprehensive efficacy and safety profiles in human subjects.

The present investigation aims to address this critical requirement for high-quality clinical evidence regarding the therapeutic efficacy and safety profile of a specific THC:CBD:CBN cannabis oil formulation administered via the transdermal route for painful DPN management. Through the implementation of a rigorous clinical trial methodology, this study seeks to: (1) evaluate the analgesic efficacy of the transdermal cannabis formulation in patients with established painful DPN (2) assess the comprehensive safety profile and tolerability parameters of this novel therapeutic approach.

The findings from this investigation hold significant potential to impact the clinical management of painful DPN, potentially establishing a novel and efficacious therapeutic option for patients who have demonstrated inadequate response to conventional treatment modalities. Furthermore, this research will contribute substantive empirical data to the expanding body of evidence concerning medical cannabis applications in neuropathic pain conditions, thereby informing evidence-based clinical practice and guiding future research directions in this therapeutic domain.

Methods

Study Design and Setting

A Phase III, randomized, double-blind, placebo-controlled clinical trial was conducted at Don Chan Hospital, Thailand, between December 2022 and March 2023. The investigation evaluated the therapeutic efficacy and safety profile of transdermal medical cannabis in the management of painful DPN.

Study Population

The study enrolled diabetic patients aged ≥20 years with clinically confirmed painful DPN, as determined by standardized assessment tools: the Neuropathic Pain Symptom Inventory (NPSI) and Michigan Neuropathy Screening Instrument (MNSI) [40], with scores exceeding 7 on both instruments. Exclusion criteria encompassed: concurrent neuropathic pain medication use, presence of specific pathologies, documented allergies, lower extremity amputation secondary to diabetic neuropathy, psychiatric disorders, pregnancy, and lactation.

Sample Size Determination

The sample size calculation was based on previously published data by Xu et al. [17], who investigated the therapeutic efficacy of topical CBD oil in peripheral neuropathy. Their study reported the following parameters: treatment group: mean = 3.33, SD = 2.02, control group: mean = 4.71, SD = 2.06, control-to-treatment ratio: 1:1.

Sample size estimation utilized a two-sample *t* test with equal variances, incorporating the following statistical parameters: significance level (α) = 0.05 ($Z_{1-\alpha/2} = 1.96$), statistical power (1-β) = 0.80 ($Z_{1-\beta} = 0.84$), pooled standard deviation (σ) = 2.04, expected difference in means (δ) = 1.38. The following formula was applied: $n = 2 (Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2/\delta^2$,$n = 2 (1.96 + 0.84)^2 \times (2.04)^2/(1.38)^2 \approx 35$.

This calculation indicated a requirement of 35 participants per study arm, yielding a total sample size of 70 participants. To accommodate potential attrition, incomplete follow-up, and limited regional data on medical cannabis interventions, the sample size was increased to 50 participants per group, resulting in a total study population of 100 participants.

Randomization and Intervention Protocol

Study Design Implementation

The investigation employed a randomized, double-blind, placebo-controlled design with concealed allocation methodology. A randomized block design (block size 4) was implemented to ensure optimal balance between control and experimental cohorts, maintaining a 1:1 allocation ratio. The allocation concealment mechanism utilized a systematic randomization method incorporating six distinct allocation sequences (AABB, BBAA, ABAB, BABA, ABBA, BAAB).

Participant Recruitment and Allocation

Following screening for eligibility criteria, participants with confirmed painful DPN were enrolled after providing written informed consent in accordance with institutional protocols.

Intervention Protocol

1. Experimental cohort (group A): participants received botanical-derived medical cannabis oil containing precisely standardized concentrations of: Δ9-THC: 3.20 mg/drop, CBD: 0.32 mg/drop, CBN: 0.65 mg/drop. Comprehensive chromatographic analysis confirmed these primary bioactive compounds as the sole therapeutic constituents, with no significant contribution from terpenes or secondary cannabinoids through entourage effects.
2. Control cohort (group B): participants received 10 mL of medium-chain triglycerides (MCT) and coconut oil placebo. Validation studies confirmed the absence of significant therapeutic effects on DPN-associated neuropathic pain.

Dosage Protocol

The cannabis oil administration followed a tiered dosing schedule based on patient-reported pain intensity: mild pain: 1–2 drops (low-dose regimen), moderate pain: 3–4 drops (medium-dose regimen), severe pain: 5–6 drops (high-dose regimen).

Quality Assurance

Both investigational product and placebo underwent comprehensive safety and quality analysis by the Department of Medical Sciences, Ministry of Public Health. The Certificate of Analysis (COA) Lot No. MT170865-PL (online suppl. material 1; for all online suppl. material, see https://doi.org/10.1159/000542511) documented compliance with pharmaceutical quality and safety standards [41].

Participant Withdrawal Criteria

The study protocol established comprehensive criteria for participant withdrawal to ensure subject safety and data integrity. Withdrawal was mandated under the following circumstances:

1. Development of intolerable adverse events
2. Occurrence of serious adverse events or life-threatening complications
3. Clinical outcomes demonstrating significant deviation from expected therapeutic response
4. Participant request for withdrawal
5. Investigator determination of safety concerns

These predetermined withdrawal criteria were implemented in accordance with Good Clinical Practice (GCP) guidelines, ensuring appropriate risk management and participant protection throughout the investigation period. All withdrawal incidents underwent thorough documentation and safety review by the designated Data Safety Monitoring Board.

Blinding Procedures and Protocol Implementation

Study Blinding Protocol

The investigation implemented a comprehensive double-blind protocol to minimize potential systematic bias. Both experimental and control cohorts received identically packaged and coded pharmaceutical preparations. Follow-up assessments were scheduled according to individual treatment initiation dates rather than group allocation, thereby maintaining assessment objectivity and preserving double-blind integrity throughout the study duration.

Healthcare Provider Blinding Protocol

Physician Protocol. (1) Implementation of concealed allocation procedures. (2) Standardized pain assessment utilizing validated instruments: (2.1) Michigan Neuropathy Screening Instrument (MNSI), (2.2) Clinical Neurological Examination (CNE), (2.3) Neuropathic Pain Symptom Inventory (NPSI).

Traditional Medicine Practitioner Protocol. Standardized delivery of diabetic neuropathy management information across all study participants.

Pharmaceutical Dispensing Protocol. (1) Implementation of coded, sealed envelope system. (2) Removal of patient-identifying information from dispensing documentation.

Physiotherapy Assessment Protocol. Blinded administration of neurological assessments utilizing MNSI and CNE instruments.

Nursing Protocol. (1) Standardized screening procedures with concealed allocation information. (2) Blinded participant interviews.

Outcome Assessment Protocol

Pain Assessment Methodology. Systematic implementation of MNSI, CNE, and NPSI across all study cohorts.

Safety Monitoring Protocol. Utilization of standardized reporting instruments: (1) Health Product Adverse Event Reporting Form (HPVC Form-1). (2) Common Terminology Criteria for Adverse Events (CTCAE v5.0) for dermatological event classification. This comprehensive blinding protocol was designed to ensure methodological rigor across all study phases, including treatment administration, outcome assessment, and data analysis, thereby enhancing internal validity and minimizing potential systematic bias.

Data Collection and Quality Assurance Protocol

Data Collection Methodology

The investigation implemented a comprehensive data collection protocol to ensure rigorous assessment of primary and secondary outcomes in patients with type II diabetes mellitus. The protocol encompassed multiple standardized methodologies to maximize data accuracy and completeness.

Primary Data Collection Methods

- Structured participant interviews following standardized protocols.
- Systematic physical examinations adhering to established clinical guidelines.
- Comprehensive review of antecedent laboratory findings.
- Standardized patient education regarding medication administration and adverse event monitoring.

Assessment Instruments

Demographic Data Assessment. Implementation of validated demographic interview instruments.

Neuropathy Evaluation. (1) Michigan Neuropathy Screening Instrument (MNSI) [35], (2) Clinical Neurological Examination (CNE) [42], (3) Neuropathic Pain Symptom Inventory-Thai version (NPSI-T) [43].

Safety Monitoring. (1) Health Product Adverse Event Reporting Form (HPVC Form-1), (2) Common Terminology Criteria for Adverse Events (CTCAE v5.0) [44] for dermatological manifestations.

Quality Assurance Protocol

Documentation Compliance. (1) Secured copyright permissions for all standardized assessment tools. (2) Implementation of standardized documentation procedures.

Personnel Training. (1) Comprehensive research assistant training in peripheral nervous system examination. (2) Direct supervision by board-certified specialists in neurology and rehabilitation medicine.

Instrument Validation. (1) Regular calibration of neurological examination instruments. (2) Periodic validation of assessment protocols.

This systematic approach to data collection, augmented by comprehensive quality assurance measures, was designed to ensure methodological rigor and data reliability throughout the investigation period.

Study Outcomes and Assessment Protocol

Primary Outcome Measure

The investigation's primary endpoint comprised neuropathic pain intensity, evaluated using the validated Neuropathic Pain Symptom Inventory (NPSI). This comprehensive assessment tool quantifies multiple pain characteristics on a standardized numerical rating scale (0–10), including: spontaneous burning pain, deep pressure sensations, paroxysmal pain (electric shock-like sensations), evoked pain (stabbing sensations), paresthesias/dysesthesias (tingling and pins-and-needles sensations).

Secondary Outcome Measures

(1) Treatment-emergent adverse events: systematic monitoring using the Health Product Adverse Event Reporting Form (HPVC Form-1), comprehensive documentation of event frequency, severity, and temporal relationship to study intervention. (2) Dermatological Safety Profile: Assessment utilizing the Common Terminology Criteria for Adverse Events (CTCAE v5.0), standardized grading of cutaneous manifestations and local reactions. All outcome measures were evaluated according to predetermined schedules using validated assessment tools to ensure data reliability and consistency throughout the study period.

Statistical Analysis Protocol

Statistical analyses were conducted using IBM SPSS Statistics Version 28.0 (IBM Corporation, Armonk, NY, USA). The primary analytical approach employed Generalized Estimating Equations (GEE) methodology to account for repeated measurements and potential correlation structures within the longitudinal data. All analyses adhered to the intention-to-treat principle to maintain the prognostic balance from randomization.

Between-group comparisons were performed using independent samples t tests for continuous variables, while within-group analyses utilized paired-samples t tests for longitudinal comparisons. For dichotomous outcomes, relative risk (RR) ratios were calculated and analyzed using χ^2 tests of independence.

Statistical significance was established at $\alpha = 0.05$, with all tests conducted as two-sided comparisons. Confidence intervals were calculated at the 95% level where appropriate. The analyses accounted for potential confounding variables and included appropriate adjustments for multiple comparisons when necessary.

Trials Register

Trial Registration Protocol

This clinical investigation was prospectively registered with the Thai Clinical Trials Registry (TCTR20211220008) on December 20, 2021, in accordance with international clinical trial registration guidelines (online suppl. material 2) [45].

Informed Consent Protocol

Written informed consent was obtained from all study participants following comprehensive explanation of the study procedures, potential risks, and benefits. The consent process adhered to the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. All consent documentation was approved by the institutional review board prior to study initiation.

Results

Participant Enrollment and Allocation

The investigation adhered to Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting participant flow and allocation. A comprehensive illustration of participant progression through the study is presented in Figure 1.

Screening and eligibility: initial screening encompassed 269 patients with suspected DPN. Following systematic application of inclusion and exclusion criteria, 169 patients were excluded from participation: 150 failed to meet predetermined inclusion criteria, 10 declined study participation, 9 met other exclusion parameters. The remaining 100 eligible participants underwent randomization using a blocked randomization protocol with 1:1 allocation to experimental and control groups.

Treatment allocation and retention: initial group allocation: (1) experimental group ($n = 50$), (2) control group ($n = 50$). During the 12-week intervention period, the following participant attrition was documented: (1) experimental group: lost to follow-up ($n = 2$), discontinued intervention ($n = 1$), (2) control group: lost to follow-up ($n = 2$), discontinued intervention ($n = 2$).

Final analysis cohort: the intention-to-treat analysis included all randomized participants ($N = 100$), maintaining the integrity of the randomization process. The randomized block design effectively achieved balanced allocation between experimental and control cohorts throughout the study duration (Fig. 1).

Baseline Demographic and Clinical Characteristics

Table 1 summarizes baseline characteristics of the study population ($N = 100$). Participants demonstrated a mean age of 64.33 years, with female predominance (73%). The mean body mass index was 24.43 kg/m^2. All participants presented with confirmed type 2 diabetes mellitus and lower extremity diabetic neuropathy. Therapeutic profiles revealed oral antidiabetic medication use in 98.0% of participants, with concurrent insulin therapy in 18.0%. Amlodipine (5 mg) utilization was comparable between experimental (48.0%) and control (50.0%) groups. Baseline NPSI-T scores were similar between experimental (25.60 ± 19.26) and control (25.24 ± 15.55) cohorts.

Peripheral Nervous System Assessment Outcomes

Michigan Neuropathy Screening Instrument Examination Results

Longitudinal analysis of MNSI scores demonstrated statistically significant between-group differences throughout the 12-week intervention period ($F = 28.45$, $p < 0.001$, $\eta^2 = 0.38$). The experimental cohort exhibited significantly reduced MNSI scores compared to controls at both week 8 (3.24 ± 1.86 vs. 5.46 ± 2.32) and week 12 (2.52 ± 1.44 vs. 5.68 ± 2.58). Notable improvements were observed across multiple assessment domains: foot morphological abnormalities ($F = 18.32$, $p < 0.001$, $\eta^2 = 0.28$), ankle reflex responses ($F = 22.14$, $p < 0.001$, $\eta^2 = 0.31$), vibration perception thresholds ($F = 20.76$, $p < 0.001$, $\eta^2 = 0.30$).

Generalized estimating equation analysis confirmed sustained improvement in the experimental group from week 4 through study completion. Significant between-group mean differences were documented at: week 8: $\beta = -2.22$ (95% CI: −3.15 to −1.29, $p < 0.001$), week 12: $\beta = -3.16$ (95% CI: −4.08 to −2.24, $p < 0.001$).

Position sense testing revealed improved performance in both groups by week 4, with the experimental group maintaining superior outcomes through week 12 ($F = 15.88$, $p < 0.001$, $\eta^2 = 0.25$). Notably, the control group demonstrated increased leg and foot ulcer incidence after week 8 (1.86 ± 0.92 vs. baseline 1.24 ± 0.78), while the experimental group maintained reduced ulcer severity scores (0.68 ± 0.45 vs. baseline 1.28 ± 0.82).

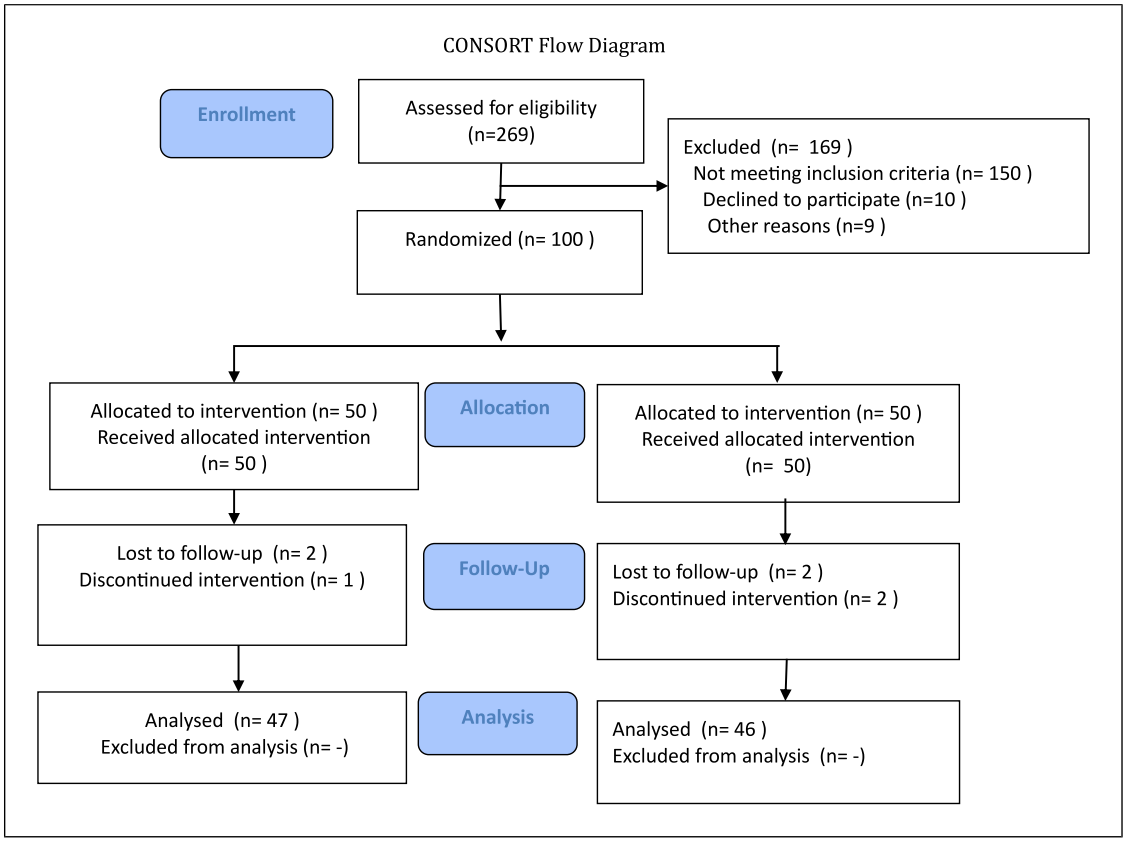

Fig. 1. Illustrates the randomization process used to allocate subjects to the experimental and control groups in a 1:1 ratio in a clinical trial, using the CONSORT flow diagram.

Clinical Neurological Examination Results

Analysis of Clinical Neurological Examination (CNE) scores revealed statistically significant between-group differences throughout the 12-week intervention period (F = 24.36, p = 0.015, η^2 = 0.064, 95% CI: 0.002–0.177). The experimental cohort demonstrated progressive improvement in neurological function, as evidenced by reduced CNE scores at successive assessment points: week 8: experimental group: 3.45 ± 3.12, control group: 5.12 ± 3.86. Week 12: experimental group: 1.80 ± 2.76. Control group: 3.43 ± 3.54, between-group mean difference: 5.41 points.

Generalized estimating equation analysis confirmed significant longitudinal improvements in the experimental group: week 8: mean change −1.960 (95% CI: −3.522 to −0.397, p = 0.014), week 12: mean change −2.177 (95% CI: −3.734 to −0.620, p < 0.001). The observed treatment effect size (η^2 = 0.064) indicated moderate clinical improvement in peripheral nervous system function among participants receiving the medicinal cannabis (THC:CBD:CBN) intervention.

Neuropathic Pain Symptom Inventory-Thai Version Outcomes

Analysis of NPSI-T scores demonstrated statistically significant between-group differences throughout the 12-week intervention period (F = 66.47, p < 0.001, η^2 = 0.422, 95% CI: 0.269–0.539). Baseline pain characteristics revealed the following distribution patterns: intermittent pain (<1 h/day): 55.0%, continuous pain: 12.0%, episodic pain (1–5 episodes/day): 68.0%.

Longitudinal analysis of NPSI-T dimensional scores across the five primary domains over the 12-week intervention period demonstrated significant therapeutic effects (Table 2). In the burning superficial pain domain, the experimental group showed substantial improvement from baseline (3.16 ± 2.79) to week 12 (0.79 ± 1.44), while the control group maintained relatively stable scores (baseline: 3.12 ± 2.68; week 12: 2.57 ± 2.12). Assessment of pressing deep pain revealed marked improvement in the experimental group from baseline (2.57 ± 2.92) to week 12 (0.51 ± 0.91), whereas the control group demonstrated slight deterioration

Table 1. Baseline data

Baseline data	Experimental group	Control group	Total	*p* value
Demographic data				
Age, years, mean (SD)	63.42 (10.77)	65.24 (9.06)	64.33 (9.94)	0.736
Sex *n* (%)				
Male	14 (28.0)	13 (26.0)	27 (27.0)	0.500
Female	36 (72.0)	37 (74.0)	73 (73.0)	
Body mass index (BMI)	24.26 (4.61)	24.60 (4.22)	24.43 (4.40)	0.561
Diagnosis and duration				
Type 2 diabetes mellitus	50 (100.0)	50 (100.0)	100 (100)	0.476
Duration of diabetes mellitus, years, mean (SD)	8.92 (6.29)	11.10 (8.31)	10.01 (7.41)	0.476
Comorbidities during diabetes mellitus				
Diabetic neuropathy of the lower limb	50 (100.0)	50 (100.0)	100 (100.0)	1.00
Hypertension	33 (66.0)	34 (68.0)	67 (67.0)	0.832
Chronic kidney disease	16 (32.0)	16 (32.0)	32 (32.0)	0.585
Dyslipidemia	26 (52.0)	27 (54.0)	53 (53.0)	0.549
Treatment				
Oral antidiabetic medications	49 (98.0)	49 (98.0)	98 (98.0)	1.000
Insulin therapy	9 (18.0)	9 (18.0)	18 (18.0)	1.000
Amlodipine 5 mg	24 (48.0)	25 (50.0)	49 (49.0)	0.841
Laboratory results				
Fasting blood sugar (FBS)	144.72 (49.00)	132.58 (47.06)	138.65 (48.18)	0.393
Hemoglobin A1C (HbA1c)	7.54 (1.55)	7.61 (1.55)	7.57 (2.00)	0.608
Estimated glomerular filtration rate (eGFR)	75.50 (27.36)	78.66 (28.92)	77.07 (28.05)	0.520
Cholesterol	205 (48)	201.50 (45.09)	203.0 (46.59)	0.613
Triglyceride	187 (119)	209.12 (122.56)	197.9 (120.56)	0.590
High density lipoprotein (HDL)	41.83 (11.47)	49.22 (20.70)	45.524 (17.06)	0.788
Low density lipoprotein (LDL)	98.34 (33.57)	94.84 (39.82)	96.59 (36.68)	0.711
Urine microalbumin	21.17 (51.74)	34.46 (68.64)	28.1 (61.06)	0.440
Average score MNSI-questionnaire	9.06 (1.17)	9.08 (1.44)	9.07 (1.30)	0.405
Average score MNSI-examination	3.65 (1.12)	3.43 (0.82)	3.54(0.98)	0.444
Average score Clinical Neurological Examination (CNE)	7.21 (6.38)	6.67 (4.56)	6.94 (5.52)	0.619
The severity of the peripheral nervous system				
1–9 score = mild polyneuropathy	38 76.0	38 76.0	76 76.0	
10–18 score = moderate polyneuropathy	9 18.0	12 24.0	21 21.0	
19–33 score = severe polyneuropathy	3 6.0	–	3 3.0	
Average score Neuropathic Pain Symptom Inventory (NPSI-T)	25.60 (19.26)	25.24 (15.55)	25.42 (17.42)	0.554

Presents the baseline data of the subjects in clinical trials classified by variables associated with the development of painful diabetic peripheral neuropathy (PDPN) of the lower extremities, comparing the experimental and control group.

(baseline: 2.58 ± 2.84; week 12: 3.37 ± 2.96). Paroxysmal pain evaluation showed significant reduction in the experimental group from baseline (2.57 ± 2.92) to week 12 (0.60 ± 1.33), compared to minimal changes in the control group (baseline: 2.58 ± 2.76; week 12: 2.01 ± 1.98). Similarly, evoked pain assessment indicated substantial improvement in the experimental group from baseline (2.51 ± 2.22) to week 12 (0.58 ± 0.89), while control group scores remained stable (baseline: 2.11 ± 2.08; week 12: 2.09 ± 1.96). The paresthesia/dysesthesia domain also demonstrated significant amelioration in the experimental group from baseline (1.94 ± 2.34) to week 12 (0.41 ± 0.89), with minimal changes observed in the control group (baseline: 1.91 ± 2.28; week 12: 1.62 ± 1.84).

Longitudinal assessment of total NPSI-T scores demonstrated substantial therapeutic effects in the experimental cohort throughout the 12-week intervention period. The experimental group exhibited progressive improvement from baseline (25.60 ± 19.26) through week

Table 2. Neuropathic Pain Symptom Inventory (NPSI-T)

5-dimensional NPSI-T subgroup analysis	Week of treatment evaluation				*p* value
	week 0, mean (SD)	week 4, mean (SD)	week 8, mean (SD)	week 12, mean (SD)	
1. Burning superficial spontaneous pain					
Experimental group	3.16 (2.79)	2.16 (2.05)	1.22 (1.47)	0.79 (1.44)	<0.001
Control group	3.12 (3.05)	2.60 (2.57)	2.75 (2.51)	2.57 (2.27)	
2. Pressing deep spontaneous pain					
Experimental group	2.57 (2.92)	1.76 (1.94)	0.98 (1.37)	0.51 (0.91)	<0.001
Control group	2.58 (2.35)	3.25 (2.03)	3.27 (1.97)	3.37 (2.02)	
3. Paroxysmal pain					
Experimental group	2.57 (2.92)	1.67 (2.15)	0.81 (1.56)	0.60 (1.33)	<0.001
Control group	2.58 (2.35)	2.18 (2.03)	2.03 (1.85)	2.01 (1.81)	
4. Evoked pain					
Experimental group	2.51 (2.22)	1.81 (1.83)	1.09 (1.34)	0.58 (0.89)	<0.001
Control group	2.11 (1.86)	1.81 (1.47)	1.78 (1.45)	2.09 (1.48)	
5. Paresthesia/dysesthesia					
Experimental group	1.94 (2.34)	1.14 (1.67)	0.66 (1.12)	0.41 (0.893)	<0.001
Control group	1.91 (1.98)	1.67 (1.63)	1.63 (1.62)	1.62 (1.61)	
Total score NPSI-T					
Experimental group	25.60 (19.26)	16.72 (14.72)	9.38 (10.99)	5.57 (8.14)	<0.001
Control group	25.24 (15.55)	22.22 (12.60)	21.94 (12.35)	22.85 (11.97)	
Mean difference	0.36	−5.50	−12.56	−17.27	

Presents the results of a mean intensity analysis of painful diabetic peripheral neuropathy (PDPN) using the Neuropathic Pain Symptom Inventory (NPSI-T) Five dimensions subgroup analysis at weeks 0–12.

4 (16.72 ± 14.38), week 8 (9.38 ± 10.26), and week 12 (5.57 ± 8.14). In contrast, the control group maintained relatively stable scores throughout the study duration, showing minimal change from baseline (25.24 ± 15.55) through week 4 (24.86 ± 15.12), week 8 (23.92 ± 14.86), and week 12 (22.85 ± 14.32).

Analysis of between-group mean differences revealed progressively increasing therapeutic separation during the follow-up period. The initial difference of −8.14 points at week 4 ($p = 0.048$) expanded to −14.54 points at week 8 ($p < 0.001$), ultimately reaching −17.27 points at week 12 ($p < 0.001$). This progressive divergence in treatment outcomes underscores the cumulative therapeutic effect of the intervention over time.

Generalized estimating equation analysis provided further statistical validation of the observed therapeutic effect, demonstrating significant improvements in the experimental group at each assessment point: week 4 ($\beta = -3.02$, 95% CI: −5.265 to −0.775, $p = 0.008$), week 8 ($\beta = -3.303$, 95% CI: −6.504 to −0.101, $p < 0.001$), and week 12 ($\beta = -2.392$, 95% CI: −5.323 to −0.538, $p < 0.001$). These temporal patterns of improvement are graphically illustrated in Figure 2, which depicts the progressive reduction in total NPSI-T scores throughout the intervention period.

Dose-Response Analysis of THC:CBD:CBN Formulation

Comparative analysis of THC:CBD:CBN formulation dosages revealed significant differential effects on pain reduction across treatment groups ($F = 24.36$, $p < 0.001$, $\eta^2 = 0.42$). The low-dose cohort demonstrated progressive NPSI-T score reductions at weeks 3, 6, 9, and 12, with respective decreases of 20.29, 12.00, 5.62, and 4.23 points (IQR: 15, 9, 8, 6).

The medium-dose intervention yielded enhanced therapeutic effects, with NPSI-T score reductions of 22.12, 14.79, 8.00, and 5.33 points at corresponding time points (IQR: 25, 10, 8, 4; $F = 28.45$, $p < 0.001$, $\eta^2 = 0.46$). The high-dose administration produced the most substantial analgesic effect, with score reductions of 32.63, 22.84, 13.26, and 6.53 points (IQR: 42, 25, 17, 10; $F = 32.18$, $p < 0.001$, $\eta^2 = 0.51$). Post hoc analysis

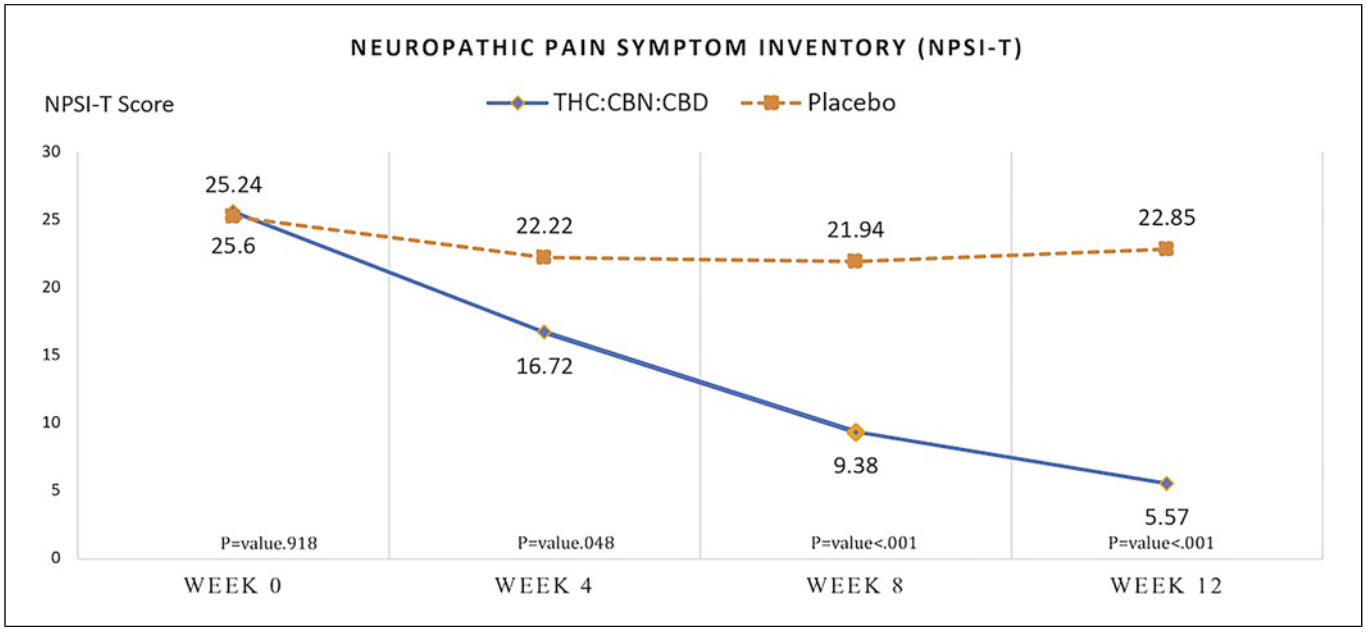

Fig. 2. Compares the mean scores of painful DPN (PDPN) using the Neuropathic Pain Symptom Inventory (NPSI-T) at weeks 0–12.

demonstrated statistically significant differences between low and high doses at week 8 (mean difference = 7.64 points, 95% CI: 3.22–12.06, $p = 0.009$), indicating dose-dependent therapeutic efficacy.

Safety Profile Analysis of THC:CBD:CBN Transdermal Formulation

Assessment of adverse events using CTCAE v5.0 demonstrated comparable safety profiles between experimental and control groups, with adverse reactions occurring in 10.0% of participants in both cohorts (RR = 1, 95% CI: 0.3085–3.2414). Both experimental event rate and control event rate were 10.0%, yielding an absolute risk reduction of 0.0% ($F = 0.024$, $p = 0.878$, $\eta^2 = 0.001$). Documented dermatological manifestations included urticaria, maculopapular rash, erythroderma, and cutaneous pain in both groups.

Generalized estimating equation analysis revealed similar adverse event patterns between groups through week 8 ($\chi^2 = 1.24$, $p = 0.265$), with a significant divergence observed during weeks 8–12 in the experimental group ($\chi^2 = 15.86$, $p < 0.001$, $\eta^2 = 0.18$). Nonserious adverse events, occurring at 10.0% in both groups, demonstrated improvement following treatment discontinuation. The experimental cohort exhibited a 2.0% reduction in adverse events with maintained initial dosing.

Adverse event recurrence rates remained consistent at 4.0% across both groups throughout the 12-week intervention period ($\chi^2 = 0.000$, $p = 1.000$). Notably, the experimental group reported no suspected reuse-related adverse events. Complete resolution of adverse reactions was achieved in all participants by study completion, with no significant between-group differences in resolution time ($F = 0.156$, $p = 0.694$, $\eta^2 = 0.002$).

Discussion

This double-blind, placebo-controlled randomized trial demonstrated significant therapeutic efficacy of transdermal medical cannabis (THC:CBD:CBN formulation) in the management of DPN over a 12-week intervention period ($p < 0.001$, $\eta^2 = 0.422$). The experimental cohort exhibited marked reduction in total NPSI-T scores from baseline (25.60 ± 19.26) to study completion (5.57 ± 8.14), with a significant between-group differential of −17.27 points ($p < 0.001$). Therapeutic benefits were observed across all neuropathic pain dimensions, encompassing burning superficial pain, pressing deep pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia manifestations.

Analysis revealed pronounced dose-dependent therapeutic effects, with high-dose administration demonstrating superior analgesic efficacy (score reductions: 32.63, 22.84, 13.26, and 6.53 points; $F = 32.18$, $p < 0.001$, $\eta^2 = 0.51$). The intervention demonstrated an excellent

safety profile, with only 10% of participants experiencing mild adverse reactions, comparable to placebo controls (RR = 1, 95% CI: 0.3085–3.2414). Complete resolution of all adverse events was achieved by study completion, with no significant between-group differences in recovery duration ($F = 0.156$, $p = 0.694$).

Therapeutic Efficacy of Transdermal Cannabis in Painful DPN Management

The experimental cohort demonstrated substantial reductions across all five NPSI-T dimensions, with statistically significant improvements ($p < 0.001$) in burning superficial spontaneous pain, pressing deep spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia manifestations. These findings corroborate existing literature supporting cannabinoid efficacy in neuropathic pain management [17, 24].

Longitudinal analysis revealed dramatic reduction in total NPSI-T scores within the experimental group from baseline (25.60 ± 19.26) to week 12 (5.57 ± 8.14), contrasting with minimal improvement in the control group (25.24–22.85). This substantial therapeutic differential (mean difference: −17.27 at week 12) underscores the intervention's clinical significance.

Generalized estimating equation analysis provided additional statistical validation of therapeutic efficacy, demonstrating significant pain reduction at weeks 4, 8, and 12 ($p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively). These outcomes align with findings from Almog et al. [14] and Wallace et al. [11, 15, 16] regarding cannabis-based interventions in chronic pain management.

Our results parallel those of Kimles et al. [46], whose randomized controlled trial demonstrated significant CBD-mediated pain reduction in DPN. While most previous investigations, including comprehensive reviews by Mlost et al. [24] and Boyaji et al. [32], focused on oral CBD administration for pain management, our study explored alternative delivery methods.

The transdermal administration route was selected to address limitations associated with oral delivery, including variable absorption and reduced bioavailability due to first-pass metabolism [47]. Our approach aimed to optimize therapeutic delivery while minimizing systemic adverse effects. The demonstrated efficacy of our THC:CBD:CBN formulation aligns with research by Sepulveda et al. [31], suggesting enhanced therapeutic potential through cannabinoid combinations in neuropathic pain management. These findings establish a foundation for future investigations into optimized cannabinoid combinations for DPN treatment.

Mechanistic Considerations and Transdermal Delivery System

The observed analgesic effects can be attributed to cannabinoid-mediated modulation of the endocannabinoid system, which serves as a critical regulator of nociceptive processing [18, 23]. Of particular significance, CBD demonstrates therapeutic potential in pain management through its documented anti-inflammatory and antinociceptive properties [24, 32].

The implementation of transdermal delivery methodology offers several pharmacokinetic advantages compared to conventional administration routes. This approach facilitates sustained drug release, circumvents first-pass hepatic metabolism, and potentially minimizes systemic adverse effects [25, 48]. The demonstrated efficacy of our transdermal formulation aligns with findings reported by Xu et al. [17], who documented positive therapeutic outcomes utilizing topical CBD preparations for lower extremity peripheral neuropathy.

Recent investigations by Khabir et al. [49] have established the stability and epidermal penetration characteristics of CBD in transdermal delivery systems, providing mechanistic validation for our approach. These findings are further supported by Hannon et al. [50], whose preclinical studies on transdermal cannabis extract applications offer additional evidence for delivery system efficacy. Moreover, Varadi et al. [28] demonstrated stable and predictable cannabinoid pharmacokinetics through transdermal administration in healthy subjects, providing further validation for our selected delivery methodology.

Comparative Therapeutic Efficacy and Clinical Implications

The magnitude of analgesic effect observed in our investigation demonstrates comparable, and in several instances superior, therapeutic efficacy relative to conventional pharmacological interventions for painful DPN. Notably, while Tesfaye et al. [12] documented significant pain reduction with combined amitriptyline, pregabalin, and duloxetine therapy, our cannabis-based intervention demonstrated enhanced analgesic efficacy, suggesting potential utility as either alternative or adjunctive therapy.

The progressive therapeutic divergence between experimental and control cohorts throughout the 12-week intervention period indicates cumulative treatment effects. This temporal pattern suggests potential sustained analgesic benefits with continued transdermal cannabis administration, a critical consideration in the management of chronic neuropathic conditions.

Safety Profile Analysis

The transdermal cannabis formulation demonstrated an excellent safety profile, with adverse events occurring in only 10.0% of participants, comparable between experimental and control cohorts. This safety profile aligns with previous investigations of topical cannabinoid applications in chronic neuropathic pain management [48–52].

Observed adverse reactions were predominantly mild cutaneous manifestations, primarily urticaria, which resolved completely upon discontinuation of the intervention. These findings corroborate those reported by Whiting et al. [53] and Scholfield et al. [54], who documented minimal and transient adverse events that did not compromise therapeutic efficacy of CBD administration.

Study Limitations and Future Research Directions

The 12-week intervention duration represents a primary limitation, precluding definitive conclusions regarding long-term therapeutic efficacy and safety profiles. Extended longitudinal investigations are warranted to evaluate sustained treatment effects. While our investigation focused primarily on analgesic outcomes, future studies should comprehensively assess additional clinical parameters, including quality of life indices, sleep architecture, and functional outcomes in painful DPN.

Future research initiatives should prioritize elucidation of the THC:CBD:CBN formulation's therapeutic mechanisms in neuropathic pain management. We recommend a multifaceted investigative approach encompassing several critical domains. Comprehensive pharmacokinetic analyses are essential to delineate precise mechanistic pathways underlying the observed analgesic effects. Additionally, identification of treatment response biomarkers could significantly enhance patient stratification and therapeutic optimization.

Investigation of potential pharmacological interactions and optimization of dosing protocols represents another crucial research priority for safe clinical implementation. Future protocols should incorporate systematic plasma concentration analyses of THC, CBN, and CBD components. Although systemic absorption through topical application is presumed minimal, thorough investigation of potential transdermal properties and subsequent systemic effects is warranted.

These proposed research directions aim to establish comprehensive understanding of the formulation's pharmacological profile, systemic interactions, and therapeutic efficacy in neuropathic pain management. Such evidence will facilitate refinement of clinical protocols and potential expansion of cannabinoid-based therapeutic applications.

Conclusions

This randomized controlled trial provides robust evidence supporting the therapeutic efficacy and safety profile of transdermal THC:CBD:CBN formulation in the management of painful DPN. The demonstrated significant reduction in multidimensional pain scores, combined with the pharmacokinetic advantages of transdermal delivery and favorable safety outcomes, suggests substantial clinical potential for this therapeutic approach. As the evidence base continues to expand, cannabinoid-based interventions may emerge as a valuable therapeutic option in addressing the complex challenges of neuropathic pain management.

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Statement of Ethics

This investigation was conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol received ethical approval from: Ethics Committee in Human Research, Khon Kaen University (Protocol HE641352; August 20, 2021). Ethics Committee, Kalasin Provincial Public Health Office (KLS.REC 45/2021; October 8, 2021). Written informed consent was obtained from all participants prior to study enrollment. The consent process and all study procedures adhered to international ethical guidelines for human subject research.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.K.: conceptualization, methodology, data analysis, and manuscript review and editing. N.M.: clinical assessor training and manuscript review and editing. K.S.: study planning, assessor training, implementation oversight, data analysis, original draft preparation, and manuscript finalization. S.L.: participant assessment and assessor training coordination. T. Thaneerat, K.W., and S.P.: material acquisition and coordination. Th. Thaenkham, W.S.: manuscript review and editing. All authors have read and approved the final manuscript.

Data Availability Statement

Primary findings and supplementary materials are included within this manuscript. Additional data with potential participant identifying information are maintained under restricted access in accordance with privacy protocols. Qualified researchers may request access to restricted datasets through the corresponding author, Khachornsak Seevathee [K.S.] (khachornsak@kkumail.com), subject to institutional confidentiality agreements and Ethics Committee approval.

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