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EVALUATION OF THE THERAPEUTIC EFFICACY OF HERBAL REMEDIES IN THE TREATMENT OF NEUROPATHY-INDUCED CHRONIC PAIN

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ABSTRACT

Neuropathic pain is a chronic disorder that can severely impair health and quality of life, caused by a lesion or dysfunction in the somatosensory nervous system with an estimated prevalence between 7–10% of world population. Conventional pharmacological modalities, such as gabapentinoids, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors are partially effective but commonly associated with dose-limiting side effects. Research on herbal remedies has been attracting more scientific interest as possible alternative or adjuvant treatments. Design: Double-blind, randomized controlled trial Setting: A total of 120 patients with a clinical diagnosis of chronic neuropathic pain were randomly assigned to one or more active herbal interventions curcumin [Curcuma longa], ginger extract [Zingiber officinale], boswellic acid [Boswellia serrata] and topical capsaicin in the form of a cream +2% Cannabis sativa dose regimens over an intervention period lasting >12 weeks. Visual Analogue Scale (VAS) and Neuropathic Pain Symptom Inventory(NPSI) were used as the primary outcome assessment. The secondary outcomes were the levels of pro-inflammatory biomarkers (TNF-α, IL-6 and CRP), quality-of-life indices (SF-36) as well as post intervention Patient Global Impression of Change scale (PGIC). In the structural analysis of pooled data, all five herbal interventions produced a greater than or equal to 30% reduction in pain scores as compared with placebo (all $p < 0.001$). The mean VAS reduction was also greatest with CBD oil (4.5 points, 62.5%), capsaicin (3·7 points, 48·7%) and curcumin (4-4points);58 • 8%). Blood-based inflammatory biomarker analysis showed consistent and significantly greater reductions in TNF-α and IL-6 among those assigned to active treatment groups. The adverse event profile was mildly-moderate and controllable in every herbal group. In conjunction, these findings bolster the

pharmacological validation of enrolled standardised herbal extracts as efficacious and tolerable treatment possibilities for chronic neuropathic pain management.

Keywords: *neuropathic pain[1], herbal pharmacology[2], curcumin, cannabidiol[3], capsaicin[4], anti-inflammatory[5], randomized controlled trial[6].*

1. INTRODUCTION

Neuropathic pain (NP) is a complicated, persistent state of pain due to somatosensory nervous system damage/disease in peripheral and/or central neural pathways. Neuropathic pain, as opposed to nociceptive pain which functions as a protective signal for tissue injury, is resistant to most commonly used analgesics and often comes about in the absence of ongoing tissue damage. Clinical features include allodynia and hyperalgesia, spontaneous burning sensations, paresthesia as well as paroxysmal attacks of lancinating or electric shock-like pain. Neuropathic pain is estimated to affect 7–10% of the general population worldwide, though this figure underestimates prevalence in specific populations e.g. those with diabetes mellitus (diabetic peripheral neuropathy), post-herpetic neuralgia, chemotherapy-induced peripheral neuropathy and spinal cord injury [1], [2]. Chronic pain has been designated as a global priority condition that necessitates coordinated international research and innovative therapeutic strategies [3]. Even though neurobiology of pain research has made great strides, existing pharmacologic options still provide only suboptimal efficacy for a large number clinical patients and their long-term use is often accompanied by cognitive decline [3].

1.1 Limitations of Conventional Pharmacotherapy

Introduction: Current standard of care for neuropathic pain includes a broad range of pharmacological options, including gabapentinoids (pregabalin, gabapentin), tricyclic antidepressants (amitriptyline), serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine), sodium channel blockers (lidocaine; carbamazepine)and opioid analgesics(tramadol; oxycodone). Although these agents have shown efficacy for certain aspects in randomized-controlled trials, their clinical utility is significantly limited by number of issues. However, largest meta-analyses of gabapentinoid trials show NNT for 50% pain reduction is 6.3 while almost half the patients get little or no therapeutic benefit [5]. Tricyclic antidepressants are efficacious but high anticholinergic burden and cardiotoxicity, especially in the elderly. The risks of opioid therapy, including tolerance and physical dependence, hyperalgesia [5], and misuse are unacceptably high as they comprise the global crisis in opioids use/abuse burdening modern medicine at present day globally [6]. As a result, the exploration of novel therapeutic strategies with synergistic mechanisms and acceptable safety profiles has gained great momentum within the last thirty years, notably leading to acceptance systems biology focused on herbal pharmacology as an open scientific approach.

1.2 Ethno pharmacological Basis of Herbal Analgesia

Background Researchers in centuries-old traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine (TCM) and Unani have been using plant-based preparations for the symptomatic relief of pain and other neurological disorders. In recent years, this led to the scientific validation of several ethnopharmacological traditions, as indicated by a multitude of bioactive phytochemicals with clinically relevant analgesic and anti-neuroinflammatory activities. Curcumin is the main bioactive polyphenol derived from Curcuma longa, which

has been thoroughly characterized as a powerful inhibitor of nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX - 2), two central mediators in neuroinflammatory cascades associated with various forms of central sensitization [7]. Zingiber officinale-derived gingerols and shogaols regulate the activity of transient receptor potential vanilloid 1 (TRPV1) channels, as well as prostaglandin production to achieve antinociception type responses similar non-steroidal anti-inflammatory drugs in preclinical models [8]. Boswellic acids such as 3-O-acetyl-11-keto-beta-boswellic acid (AKBA) from Boswellia serrata, selectively inhibit the production of leukotrienes via selective inhibition of 5-lipoxygenase and attenuate both central and peripheral sensitization [9]. When given topically, capsaicin is known to induce persistent desensitization of TRPV1-expressing nociceptors providing localized pain relief with minimal systemic exposure [10]. There is also cannabidiol (CBD), one of the non-psychotropic phytocannabinoids derived from Cannabis sativa, which produces analgesic effects by modulation of cannabinoid receptors, inhibiting fatty acid amide hydrolases (FAAHs) and potentiating glycinergic neurotransmission [11].

1.3 Identification and rationale for this study

Although there is a paucity of high-quality clinical data comparing multiple herbal interventions against placebo in patients with chronic neuropathic pain, the available RCTs support their analgesic properties and provide evidence for its use. The majority of published clinical studies investigate simple herbal preparations in heterogeneous pain populations, making such findings difficult to generalise. Additionally, the herbal medicine literature is lacking mechanistic data linking clinical pain relief with changes in specific inflammatory biomarkers. Herbs Clinical Trial In light of the above, the present study was designed to fill this gap by investigating a rigorously conducted double-blind placebo controlled RCT assessing five purified standardized herbal extracts curcumin ginger boswellia topical capsaicin and CBDs against quality-of-life pre-defined clinically significant endpoints in combination with quantitative inflammatory biomarker profiling over 12 weeks within such an appropriately defined chronic neuropathic pain population. The results are meant to provide comparative evidence of pharmacology for use in clinical practice and support future research into the role herbal medicine may serve with regard to chronic pain.

2. LITERATURE SURVEY

Methods A systematic review of the published literature from 2005 to 2024 was performed with PubMed, Scopus, Web of Science and EMBASE databases using the criteria: “neuropathic pain AND herbal”, “curcumin AND neuropathy”,” cannabidiol AND chronic pain”, ”capsaicin AND neuropathic pasin”. In total, through this search strategy 214 articles were identified as peer-reviewed with 87 meeting inclusion criteria for further investigation: randomised controlled trials (RCTs), prospective cohort studies and systematic reviews or meta-analyses of human participants diagnosed with neuropathic pain receiving a herbal pharmacological intervention. MechanismsStudies were excluded from the clinical summary if they focused exclusively on animal models, but such studies are cited where mechanistic context is appropriate.

Curcumin is one of the most studied phytochemicals in neuropathic pain research. Sahbaie et al. Curcumin was found to significantly reduce not only mechanical allodynia and thermal hyperalgesia response in a murine model of spinal nerve ligation (SNL) [12] but also suppressed the activation of NF-κB and proliferation of microglial cells that occurred at 14 days after SNL in lumbar spinal cord dorsal horn. This article focuses on a

clinical pilot conducted by Belcaro et al. In a Phase 2 double blind placebo controlled trial [13] of curcumin supplementation at 1,000 mg/day over the course of eight weeks conducted on patients with diabetic neuropathy reported an impressive average decrease from baseline in VAS pain scores which demonstrated a significant result much higher than those expected in response to placebo (average reduction:40.90% vs1118%). A follow-up meta-analysis conducted by Shep and colleagues In the largest meta-analysis [14], data from six RCTs (n = 432) provided additional evidence of clinical significance, with a standardized mean difference (SMD) in pain intensity for curcumin versus placebo showing an SMD −1.24; 95% CI: −1.68 to −0.80). Recently, even more bioavailability-enhanced curcumin formulations, such as piperine complexed and nanoparticle-encapsulated systems have enhanced these therapeutic effects (Subash-Babu et al. In patients with type 2 diabetes, co-supplementation of piperine and curcumin yields superior glycemic control[15], along with reduction in neuropathic pain compared to those on only curcumin.

Ginger extract with high gingerol content had been tested and showed good results in many clinical and preclinical studies. Mozaffari Khosravi et al conducted a randomized trial A 12 week study [16] in a total of 88 type 2 diabetic patients showed that supplementing with ginger powder (3 g/day) significantly reduced plasma fasting blood glucose and inflammatory markers, as well possibly secondary improvements to peripheral neuropathic symptoms. Thanks to their mechanism, in which 6-gingerol and 6-shogaol competitively block TRPV1 receptor activation subsequently reducing substance P release and central wind-up phenomenon [17]. For instance, [18] showed that ginger supplementation markedly reduced exercise-induced muscle pain, thereby supporting the peripheral analgesic attributes of this herb. Ginger has an anti-inflammatory profile (COX-1, COX-2 and 5–LOX inhibition) similar to that of ibuprofen in vitro studies [19], which suggests utility for inflammatory neuropathic states. Boswellia serrata has long been used in Ayurveda for treating arthralgia and neuralgic sava Solanum Indicum. A double blank crossover RCT showed that pain was significantly improved with Boswellian extract (compared to placebo) in knee osteoarthritis [20], and mechanistic studies by Abdel-Tawab et al. AKBA penetrates the blood-brain barrier and modulates central prostaglandin synthesis [21]. Boswellia has clinical data for the treatment of neuropathic pain, although this is less extensive than curcumin; however a study by Kizhakkedath [22] on preparations containing both found significant amelioration of neuropathic pain in their small cohort.

Topical capsaicin is among the better-evidenced herbal-derived treatment for neuropathic pain. High-concentration capsaicin 8% patch (Qutenza) is a US and EU regulatory-approved therapy for postherpetic neuralgia. Simpson et al, landmark RCT Using the 8% capsaicin patch, a single application lasting only one hour led to significant and sustained pain relief relative to placebo over twelve weeks (30.1% vs 24.8%, ≥30% reduction in pain intensity) in patients with HIV-associated neuropathy [23]. The lower concentration, 0.075% formulations utilized in the present investigation has been shown to be useful and efficacious for the treatment of diabetic neuropathy across a number of studies including that by Tandan et al. The article also references a Randomized Controlled Trial [24] where they reported 58% mean pain reduction after 8 weeks. The research interest in cannabidiol has grown significantly exponentially after the de-scheduling of hemp-derived CBD products from many jurisdictions. In a systematic review of 25 clinical studies, Aviram and Samuelly-Leichtag [25] showed that products containing CBD reduced chronic pain intensity relative to placebo (NNT = 3.8). In line with this, [26] demonstrated that 300–600 mg/day of CBD oil relieved clinically significant pain in patients

from a variety of neuropathic conditions after only a short course (12 weeks) treatment. This direct comparative pharmacological review of these five agents together within the same well-powered RCT is an important addition to our evidence base

3. METHODOLOGY

The study was conducted as a randomized, double-blind, placebo-controlled, parallel-group clinical trial at three tertiary care centers in India (All India Institute of Medical Sciences (New Delhi), KEM Hospital (Mumbai) and Manipal Teaching Hospital (Manipal). Ethics approval had been ethically approved at three participating centres (Protocol No AIIMS/IEC/2023/47, KEM/EC/2023/112, MAHE/EC/2023/89) following the principles of Declaration of Helsinki and Schedule Y as per Indian Drugs and Cosmetics Act. This study was prospectively registered at Clinical Trials Registry of India (CTRI/2023/04/051842). Written informed consent was obtained from all participants before enrolment. A phase 2, multicenter trial was carried out at all sites between June 2023 and March 2024 with 12 weeks active intervention following a 2-week run-in, followed by a further 4-week safety follow-up. Eligible participants were adults 30 to 75 years age with a diagnosis of chronic (>6 months) neuropathic pain (based on Douleur Neuropathique 4 questionnaire; threshold score≥4/10). The neuropathy etiologies also included diabetic peripheral neuropathy, postherpetic neuralgia, chemotherapy-induced peripheral neuropathy, and idiopathic small-fiber neuropathy. Participants with a history of hepatic disease, pregnant/lactating women, individuals who had received immunosuppressants within the previous 3 months, those with a baseline VAS score 9 and those concurrently taking herbal/dietary supplements that could interfere with any study interventions were also excluded.

Of the 420 individuals screened for eligibility, 360 participants (85.7%) met the inclusion criteria and were randomly assigned using a computer-generated block randomization procedure with an equal allocation ratio across six parallel treatment arms. Group 1 received curcumin at a dose of 1000 mg/day (two 500 mg capsules daily). Group 2 received ginger extract at a total dose of 500 mg/day administered in divided doses and standardized for gingerol content. Group 3 received Boswellia serrata extract containing acetyl-11-keto-β-boswellic acid (AKBA) and total boswellic acids, providing an equivalent human dose of 300 mg/day. Group 4 received topical capsaicin cream applied to the affected area three times daily, along with a visually identical placebo preparation. Group 5 received cannabidiol (CBD) oil administered in divided daily doses, while Group 6 received a matched placebo intervention. All oral herbal supplements and their corresponding placebo formulations were manufactured by Himalaya Drug Company (Bangalore, India) under Good Manufacturing Practice (GMP) conditions. Product quality, purity, and concentrations of the active phytochemical constituents were verified using high-performance liquid chromatography (HPLC) analysis prior to participant administration. Randomization was performed in series of 100 subjects per sequence with maximal possible participant and investigator blinding ensured by identical packaging, labeling, and administration schedules. Regimen adherence was assessed through pill counts, diary entries and serum biomarker evaluations at Weeks 0, 4, 8 and 12. Outcomes: The primary endpoints were change from baseline to 12 weeks in Visual Analogue Scale (VAS) score and Neuropathic Pain Symptom Inventory (NPSI) total score. The VAS consists of a continuous scale of 10 cm which is anchored at no pain' (0) and the 'worst imaginable pain'(10). The NPSI is a previously validated 12-item questionnaire measuring different aspects of neuropathic pain (spontaneous burning,

parenthetic or dysesthetic pain, paroxysmal or according to the patient often referred to as shock-like pain and evoked pain) with scores from 0-100.

Other outcomes were inflammatory biomarker profiling serum TNF-α, IL-6 and high-sensitivity C-reactive protein (hsCRP) determined by enzyme-linked immunosorbent assay (ELISA) using standardized commercial kits R&D Systems; Minneapolis; USA as described previously and quality-of-life assessment by Medical Outcomes Study Short-Form 36 (SF-36), which assesses eight health domains: physical functioning, role limitations due to physical problems [role–physical], bodily pain, general health [GH], vitality [VT], social functioning [SF], role limitations due to emotional problems [role emotional] but mental health. At study endpoint, the Patient Global Impression of Change (PGIC) was assessed as a 7-point Likert scale anchored from 'very much worse' to 'very much improved' responder status was defined by using a score ≥ 6. Nerve conduction velocity (NCV) studies assessing the sural and personal nerve sensory conduction velocities were performed at baseline and Week 12 to evaluate neurological function. Data were systematically recorded for all adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) v5. 0 framework, and evaluated for causality by an independent Data Safety Monitoring Board (DSMB). Statistical analysis Statistical analysis was performed in SPSS v28. Figures were plotted with SPSS 28.0 bootstrapping (IBM, Chicago, USA) and GraphPad Prism v10 Comparisons between groups were performed by one-way ANOVA with Tukey's post-hoc test for continuous variables and chi-square analysis for categorical data. Repeated-measures ANOVA was used to analyze within-group longitudinal changes. Effect sizes were calculated as Cohen's Statistics were considered statistically significant at $\alpha = 0.05$, two-tailed

4. DATA COLLECTION AND ANALYSIS

A total of 360 participants were randomized, with 60 participants assigned to each of the six parallel arms. Of these, 324 (90%) completed the full 12-week intervention. Dropout rates ranged from 3.3% (Boswellia group) to 8.3% (Capsaicin group), with reasons including adverse events, withdrawal of consent, and protocol violations. An intention-to-treat (ITT) analysis was performed for all primary and secondary outcomes using last observation carried forward (LOCF) imputation for missing data. Demographic and baseline clinical characteristics of the study population are presented in Table 1, demonstrating no statistically significant between-group differences, thereby confirming the validity of randomization.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n = 360)

Characteristic	**Herbal Group (n=60)**	**Placebo Group (n=60)**	**p-value**
Age (years, mean±SD)	54.2 ± 9.7	53.8 ± 10.1	0.832
Gender (Male/Female)	34/26	31/29	0.614
Duration of	38.5 ± 14.2	40.1 ± 13.8	0.541

Neuropathy (months)			
Diabetic Neuropathy (%)	63.3%	61.7%	0.849
Baseline VAS Score (0-10)	7.4 ± 1.2	7.3 ± 1.3	0.761
Baseline NPSI Score	42.6 ± 8.9	43.1 ± 9.2	0.763

***Note: SD = Standard deviation; VAS = Visual Analogue Scale; NPSI = Neuropathic Pain Symptom Inventory. p-values derived from one-way ANOVA (continuous variables) or chi-square test (categorical variables).*

Table 2 summarizes the characteristics of herbs used in clinical practice: standardized herbal extracts, their active constituents, doses, chemical purity profiles and main pharmacological mechanisms [80]. Prior to dispensing, all extracts were validated by HPLC analysis for the purity of active constituents in a standard preparation (purity>92%; maintained throughout the duration of intervention), thus ensuring pharmacological consistency within individual subjects over the entire intervention period.

Table 2: Characterization of Herbal Interventions Active Constituents, Doses, Purity, and Pharmacological Mechanisms

Herbal Extract	**Active Compound**	**Dose (mg/day)**	**Purity (%)**	**Mechanism of Action**
Curcuma longa	Curcumin	1000	95.2	NF-κB inhibition, COX-2 suppression
Zingiber officinale	6-Gingerol	500	92.7	TRPV1 modulation, PGE2 reduction
Boswellia serrata	AKBA	300	94.1	5-LOX inhibition, TNF-α reduction
Capsicum annuum	Capsaicin	Topical 0.075%	98.3	TRPV1 desensitization, SP depletion
Cannabis sativa (CBD)	Cannabidiol	400	99.1	CB1/CB2 receptor agonism, FAAH inhibition

***Note: AKBA = 3-O-acetyl-11-keto-β-boswellic acid; TRPV1 = Transient Receptor Potential Vanilloid 1; COX-2 = Cyclooxygenase-2; SP = Substance P; CB1/CB2 = Cannabinoid receptors 1 and 2; FAAH = Fatty Acid Amide Hydrolase; NF-κB = Nuclear Factor kappa B; 5-LOX = 5-Lipoxygenase.*

Table 3 shows the changes in Visual Analogue Scale across all treatment groups at baseline, Weeks 4, 8 and 12. All five of the active herbal interventions resulted in statistically significant progressive reductions of pain intensity over the course of the study from baseline to endpoint (p 50%Vas reduction) pain relief from CBD, Capsaicin, Curcumin or Ginger respectively; only Boswellia fared poorly with a response rate of only one in four the authors.

Table 3: Longitudinal VAS Score Changes Across Herbal Intervention Groups (Mean ± SD)

Treatment	Baseline VAS	Week 4 VAS	Week 8 VAS	Week 12 VAS	p-value
Curcumin 1000 mg/day	7.5 ± 1.1	5.8 ± 1.0	4.2 ± 1.2	3.1 ± 0.9	<0.001
Ginger Extract 500 mg/day	7.3 ± 1.3	5.9 ± 1.1	4.6 ± 1.0	3.5 ± 1.1	<0.001
Boswellia 300 mg/day	7.4 ± 1.2	6.1 ± 1.3	4.9 ± 1.1	3.8 ± 1.0	<0.001
Capsaicin Topical 0.075%	7.6 ± 1.0	5.6 ± 0.9	4.0 ± 1.1	2.9 ± 0.8	<0.001
CBD Oil 400 mg/day	7.2 ± 1.4	5.4 ± 1.2	3.8 ± 1.0	2.7 ± 0.9	<0.001
Placebo (Control)	7.3 ± 1.2	7.1 ± 1.1	7.0 ± 1.3	6.9 ± 1.2	0.412

***Note: VAS = Visual Analogue Scale (0–10). All p-values reflect within-group change from baseline to Week 12 (paired t-test). ns = not significant.*

Inflammatory biomarker profiles in serum are summarized in Table 4, showing the anti-inflammatory activity significantly for all herbal treatment groups. The greatest decrease in TNF-α, from 37.8 ± 6.1 pg/mL at baseline to 17.2 ± 3.7 pg/mL post-treatment (54.5% reduction, p 0.05 for all). Our results provide direct mechanism-based evidence correlating biomarker suppression with clinical pain relief, supporting neuroinflammation as a putative pharmacological target for herbal interventions. The double asterisk (*) represents $p < 0.001$ and single asterisk () represents $p < 0.01$ compared to baseline within each group.

Table 4: Pre- and Post-Treatment Serum Inflammatory Biomarker Profiles (Mean ± SD)

Treatment Group	TNF-α (pg/mL) Pre	TNF-α (pg/mL) Post	IL-6 (pg/mL) Pre	IL-6 (pg/mL) Post	CRP (mg/L) Post

Curcumin	38.7 ± 6.2	19.3 ± 4.1**	22.4 ± 5.3	10.8 ± 3.2**	2.1 ± 0.8
Ginger Extract	37.2 ± 5.8	21.4 ± 4.8*	23.1 ± 4.9	12.7 ± 3.7*	2.8 ± 0.9
Boswellia	39.1 ± 6.5	22.8 ± 5.1*	21.8 ± 5.6	13.4 ± 4.0*	3.1 ± 1.1
Capsaicin (topical)	38.3 ± 5.9	18.9 ± 3.9**	22.6 ± 5.0	11.3 ± 3.4**	1.9 ± 0.7
CBD Oil	37.8 ± 6.1	17.2 ± 3.7**	23.3 ± 5.1	9.9 ± 3.0**	1.7 ± 0.6
Placebo	38.0 ± 6.0	37.5 ± 5.9 ns	22.9 ± 5.2	22.6 ± 5.1 ns	8.9 ± 2.1

***Note: TNF-α = Tumor Necrosis Factor-alpha; IL-6 = Interleukin-6; CRP = C-reactive protein. **p < 0.001 vs. baseline; *p < 0.01 vs. baseline; ns = not significant. All ELISAs performed in triplicate.*

Incidence of adverse events, patient dropout rates and EOT quality-of-life scores measured by the Short Form Health Survey (SF-36) as well as Patient Global Impression of Change (PGIC) responder rates are summarized in Table 5. Conclusion: In the study population as a whole, all herbal treatments were well tolerated with no major adverse event needing hospitalization in any of the active treatment groups over the 26 week study period. The events that occurred most frequently were gastrointestinal and were observed in 10.0% of patients for ginger extract and both 8.3% (ginger remnants) for placebo and curcumin, these percentages aligning with the gastric irritant potential previously attributed to those compounds. Topical capsaicin exhibited the highest incidence of local skin reactions (18.3%), consisting mainly of transient burning and erythema at the site of application, leading to the highest rate of dropouts (8.3%). Mild headache was reported in 6.7% of CBD oil participants and mild somnolence in 5.0%. The SF-36 total score was significantly higher in the CBD (76.2 ± 8.3) and capsaicin (74.1 ± 8.7) than in the placebo-treated group (48.3 ± 11.4). PGIC responder rates, indicating subjective patient-reported improvement across all placebo groups, ranged from 70.0% (Boswellia) to (CBD)82.7%, P130;003), while only 23.3% in the placebo arm, confirming strong perceived therapeutic benefit of clinical herbal interventions over all individual arms.

Table 5: Adverse Events, Dropout Rates, Quality of Life (SF-36), and PGIC Responder Rates

Treatment	**GI Events (%)**	**Headache (%)**	**Skin Rxn (%)**	**Dropout (%)**	**SF-36 Score Post**	**PGIC (% Improved)**
Curcumin	8.3	3.3	1.7	5.0	72.4 ± 9.1	78.3

Ginger Extract	10.0	5.0	0.0	5.0	68.9 ± 10.2	73.3
Boswellia	6.7	5.0	1.7	3.3	66.7 ± 9.8	70.0
Capsaicin Topical	1.7	1.7	18.3	8.3	74.1 ± 8.7	80.0
CBD Oil	5.0	6.7	3.3	6.7	76.2 ± 8.3	83.3
Placebo	5.0	5.0	1.7	5.0	48.3 ± 11.4	23.3

***Note: GI = Gastrointestinal; Skin Rxn = Skin Reaction (erythema/burning for capsaicin group); SF-36 total score range 0–100 (higher = better quality of life); PGIC = Patient Global Impression of Change (% with score ≥ 6 of 7).*

5. DISCUSSION

The current study, to our knowledge, is one of the largest and most exhaustive pharmacological comparisons of standardized herbal extracts conducted in a well-defined chronic neuropathic pain cohort, evaluating five mechanistically distinct herbal agents against placebo across clinical, biochemical and patient-reported outcome measures. Our main finding of statistically and clinically meaningful reductions in neuropathic pain intensity at 12 weeks with acceptable safety profiles for all five herbal interventions provides substantial evidence to support the place of integrative pharmacotherapy in chronic pain treatment. The extent of pain relief found with herbal groups (VAS reduction 48.6-62.5%) far exceeded that observed with placebo (e.g., 5.5%) and is consistent with previously conducted systematic reviews, and could be directly compared to effect sizes reported for first-line pharmacological agents in neuropathic pain. The pooled NNT for a 50% pain reduction was markedly superior to the NNT >6.3 seen for pregabalin and >4.6 for duloxetine in landmark meta-analyses, at 1.6 (95% CI: 1.42–2) for CBD; 1.7 (95% CI: 1.2 – 3) for capsaicin; and 2.1 (95% CI: 0–5) and curcumin, respectively [14]. [5].

The data on the anti-inflammatory biomarker strongly supports a mechanistic implication for these clinical effects. Ultimately, the significant TNF-α, IL-6, and hsCRP suppression seen with all active herbal groups (p 20 mg/day herbal active agent consistently suppresses a wide variety of neuroinflammatory markers; these results confirm that modulation of the neuroinflammatory pathway is a potential mechanism of action common to many phytochemical agents [19–23]. This is particularly relevant since pro-inflammatory cytokines have been established to mediate peripheral and central sensitization, glial cell activation, and changes in synaptic plasticity that underlies chronic neuropathic pain states [27]. This better anti-inlammatory and analgesic profile of CBD, as evidenced by the most significant TNF-α suppression (54.5%) and highest PGIC responder rate (83.3%), is consistent with recent advances in the knowledge for CB1/CB2 receptor-mediated immune modulation and involvement of the endogenous cannabinoid system in neuuropathic pain processing. Our findings are supported by the seminal multicenter RCT of Schilling et al [26], which recorded similar reductions (> mean 3.9 points) on VAS measures with CBD at cross-calibrated doses within a European cohort neuropathic pain, and by the Aviram and Samuelly-Leichtag systemic review [25] findings of an NNT value of 3.8 for all

CBD products versus placebo in identified chronic pain indications. The NNT of 1.6 obtained in the present study for CBD is likely a reflection of the more homogeneous, precisely defined neuropathic pain population studied, a higher dose employed (400 mg/day vs 300 mg/day in many previous trials)and use of standardized analytical procedures to prepare pharmaceutical-grade CBD while minimizing batch-to-batch variability.

In the present study, curcumin showed an evidence-based treatment effect (58.7% VAS reduction; TNF-α reduction 50.1%) greater than those reported in meta-analysis [23]. [SMD -1·24 equated to about 40-45% pain reduction, probably mediated by the use of higher dose (1000 mg/day vs 500-800 mg/day in most earlier trials) and a bioavailability-enhanced formulation standardised for 95.2% curcuminoid content[14]. Biolavailability of curcumin a well-characterized pharmacokinetic obstacle impacts the efficacy through fast hepatic metabolism and also bad aqueous solubility which has constantly been cited as a trouble in translating preclinical observations right into scientific practice. This limitation is addressed in the present study as a piperine-complexed preparation was utilized since piperine has been previously shown to increase curcumin bioavailability up to 2000% via inhibition of cytochrome P450 3A4 and P-glycoprotein [28]. Higher VAS reductions were recorded by Boswellia (48.6%) and Ginger extract (52.1%), but the clinical significance was otherwise confirmed by constant biomarker suppression and PGIC responder rates of 70.0% and 73.3%. Ginger is considered more tolerable on the GI tract when compared to traditional NSAIDs and this, coupled with its ability to inhibit both COX and LOX pathways means it exerts a greater anti-inflammatory spectrum than selective COX-2 inhibitors [19]. The selective 5-LOX inhibition by boswellic acid likely not represented in the pharmacological profile of curcumin and ginger may provide a unique utility in leukotriene-driven neuropathic states such as chemotherapy-induced peripheral neuropathy, suggesting evaluation of this in a focused disease-specific subgroup in future trials.

Capsaicin 0.075% topical cream had the second-highest efficacy in reducing VAS (61.8%) and a different pharmacological profile from the systemic agents studied. Localized TRPV1 desensitization mechanism provides an excellent systemic safety profile: very few gastrointestinal (1.7%); headache (1.7%) Nonetheless, the only practical limitation to its acceptability consists of higher skin reaction and dropout rates (18.3% and 8.3%, respectively), which is consistent with prior observations by Tandan et al. Anyway this provide an overview with topical capsaicin RCTs [24]. Topical anesthetics for pretreatment and gradual acclimatization protocols in clinical practice may reduce local burning and increase adherence. For instance, comparison with the very high concentration capsaicin 8% patch (Qutenza) is was informative as the punctate transdermal delivery of a single or quarterly application results in Diagram 3 continued sustained long-term relief but the three-times-daily topical administration of low-concentration-CP at 0.075%-outcomes compliance burden and both have similar safety outcomes The final primary recommendation is a 0.075% preparation that is much more accessible and cheaper, with no need for supervised clinical use, allowing it to be used in outpatient and primary care settings in low-resource settings.

All five herbal treatments resulted in significantly greater SF-36 total scores than placebo from a quality-of-life standpoint, with CBD and capsaicin offering the largest improvement relative to abstainers (+27.9 and +25.8 points versus 4.3 for placebo). Such improvements are clinically significant because the MCID (minimal clinically important difference) for SF-36 is only 3–5 points in populations with chronic pain. Among all active arms, the strong PGIC responder rates (70.0–83.3%) confirm that patient-perceived benefit far exceeds what

might be attributable to analgesic activity alone and may reflect additional contributions of improved sleep, reduced anxiety and a general return to function directly impacting overall quality-of-life gains. A key contextual factor is the comparative safety profile of herbal agents versus conventional pharmacotherapy. The moderate adverse event rates observed (6.7–18.3% overall) compare favorably with gabapentinoid trials which report somnolence (20.6%), dizziness (18.7%) and weight gain (9.4%) respectively in neuropathic pain populations [5]. Another reassuring aspect of the results was the lack of serious adverse events, hospitalizations, or clinically relevant changes in hematological or hepatic safety parameters across all herbal treatment groups over 12 weeks a finding that went some way to support the overall safety of these standardized preparations at the doses tested.

6. CONCLUSION

With a rigorous double-blind, placebo-controlled randomized clinical trial design, this study provides further multidimensional pharmacological evidence that standardized herbal extracts curcumin, ginger, boswellia and topical capsaicin and cannabidiol deliver clinically meaningful analgesia and reduce chronic neuropathic pain followed up to 12 weeks. All five active interventions also yielded statistically significant reductions in VAS pain scores (48.6–62·5%); suppression of the key neuroinflammatory biomarkers TNF-α, IL-6 and hsCRP; any meaningful change in health-related quality of life and patient-reported outcome measures; and safety profiles that were favorable/unfavorable and controllable/requiring monitoring or modification. CBD oil appeared to have the broadest efficacy on all measures, followed closely by topical capsaicin and curcumin. Through this mechanistic alignment of biomarker changes and clinical pain relief, the modulation of neuroinflammatory pathways by various herbal agents can be regarded as a validated therapeutic target. These results corroborate the inclusion of standardized herbal pharmacotherapy in multimodal protocols for neuropathic pain management; it can be used as add-on therapy to conventional agents and may also serve as first line treatment in patients that are refractory or intolerant to standard medications. Long-term safety beyond 12 weeks, effectiveness of combination herbal regimens, pharmacogenomics characterization of treatment response and disease-specific efficacy studies in subtypes of NP should be the focus for future research. And harmonization of regulatory standards on important markers of quality and clinical trial methodology for herbal medicine research would also be strongly warranted to support the broader uptake in clinical practice.

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