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Evaluating the Effectiveness of Pterocarpus santalinus (Sandalwood) Bark Extract in Managing Tension-Type Headaches: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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ABSTRACT

Background: *Tension-type headache (TTH) is the most prevalent primary headache disorder worldwide and a major cause of disability. Despite its burden, current pharmacologic options have limited efficacy and tolerability, prompting exploration of safe, plant-based alternatives. Pterocarpus santalinus bark extract possesses antioxidant and anti-inflammatory properties that may mitigate both peripheral and central mechanisms of pain sensitization.* ***Objective:*** *To evaluate the effectiveness of Pterocarpus santalinus bark (PSB) extract in reducing pain intensity and frequency among patients with tension-type headache.* ***Methods:*** *A pragmatic, randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted in Lahore, Pakistan, enrolling 80 adults aged 18–65 years diagnosed with TTH. Participants were randomly allocated (1:1) to receive either PSB extract (100 mg/mL, 250 mL three times daily) or placebo for one week. The primary outcome was change in Visual Analogue Scale (VAS) pain score, analyzed using repeated-measures ANOVA.* ***Results:*** *Baseline characteristics were comparable between groups. The PSB group showed a significant reduction in mean VAS scores from 6.22 ± 1.03 to 0.48 ± 0.51, compared to 6.10 ± 1.09 to 4.05 ± 1.01 in the placebo group ($p < 0.001$). Effect sizes were large (Cohen's $d > 2$), and 95% achieved complete pain relief. No adverse events were reported.* ***Conclusion:*** *Pterocarpus santalinus bark extract provides rapid, sustained, and well-tolerated analgesia in TTH, supporting its potential as a safe herbal adjunct to conventional therapy.*

Keywords
Pterocarpus santalinus, tension-type headache, randomized controlled trial, phytotherapy, herbal analgesic.

INTRODUCTION

Tension-type headache (TTH) represents the most prevalent primary headache disorder globally, affecting approximately 78% of the general population at some point in their lives and accounting for a considerable proportion of neurological consultations (1). According to the Global Burden of Disease (GBD) 2021 analysis, headache disorders rank among the top ten causes of disability worldwide, with nearly half of the global population reporting an active headache disorder in a given year and 15.8% experiencing headaches daily (2). In Pakistan, local studies reveal a high frequency of TTH, with one survey in Lahore identifying a 24% prevalence among adults, of whom 12% experienced chronic daily headaches (3). The disorder typically manifests during the second decade of life and exhibits a slight female predominance, with a female-to-male ratio of approximately 5:4 (4). Chronic forms of TTH markedly impair daily functioning, productivity, and psychological wellbeing, contributing to a substantial socioeconomic and healthcare burden (5).

Clinically, TTH is characterized by bilateral, non-pulsating, tightening pain that is not aggravated by physical activity and lacks the nausea or photophobia typically seen in migraine (6). The International Classification of Headache Disorders distinguishes between infrequent episodic, frequent episodic, and chronic TTH, depending on attack frequency and duration (7). Despite its prevalence, the pathophysiology of TTH remains incompletely understood. Proposed mechanisms include heightened pericranial myofascial nociception, impaired descending pain inhibition, and central sensitization leading to augmented pain perception (8). Structural and functional abnormalities within cranio-cervical musculature, such as increased trapezius trigger-point activity and restricted neck mobility, further contribute to symptom persistence (9).

Pharmacological management of TTH primarily relies on simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and prophylactic agents like tricyclic antidepressants or beta-blockers. However, long-term use of these agents carries the risk of adverse effects, including gastrointestinal irritation, medication overuse headache, and sedation (10). Given these limitations, there is increasing clinical interest in safer, plant-derived therapeutic alternatives with analgesic and anti-inflammatory potential. Traditional medical systems across South Asia have long

employed botanical preparations to alleviate headaches and muscular tension, reflecting centuries of empirical use that now warrant systematic scientific evaluation (11).

Pterocarpus santalinus, commonly known as red sandalwood, is an ethnomedicinal species belonging to the Fabaceae family and traditionally valued for its anti-inflammatory, antioxidant, and neuroprotective properties (12). Its bark and heartwood contain multiple bioactive phytochemicals such as flavonoids, santalin, pterocarpol, and phenolic acids, which collectively exert free-radical scavenging and cytokine-modulating effects (13). Preclinical investigations have demonstrated that extracts of P. santalinus reduce inflammatory markers and oxidative stress in various animal models, suggesting a potential role in alleviating neurogenic and musculoskeletal pain (14,15). Furthermore, the ethanolic extract of P. santalinus has shown inhibition of pro-inflammatory enzymes and protection against neuronal damage, reinforcing its relevance in headache pathophysiology (16).

Despite these promising findings, no clinical trial has yet evaluated the efficacy of P. santalinus bark extract in humans with TTH. Existing literature focuses primarily on its heartwood, leaving the therapeutic potential of the bark largely unexplored. Considering the burden of TTH and the need for safer, rapid-acting, and well-tolerated alternatives, exploring P. santalinus bark extract offers a scientifically plausible and clinically meaningful direction.

The present study was therefore designed as a pragmatic, randomized, double-blind, placebo-controlled clinical trial to evaluate the effectiveness of Pterocarpus santalinus bark extract (PSB) in mitigating the intensity and frequency of tension-type headaches. The hypothesis was that PSB extract would significantly reduce headache severity, measured by the Visual Analogue Scale (VAS), compared to placebo over a one-week intervention period.

MATERIALS AND METHODS

This study adopted a pragmatic, randomized, double-blind, placebo-controlled, multicenter clinical trial design to evaluate the efficacy of Pterocarpus santalinus bark (PSB) extract in reducing the intensity of tension-type headache (TTH). The trial was conducted in an urban community setting in Lahore, Pakistan, from March to July 2024, following ethical approval from the Institutional Review Board of Rashid Latif Medical College (Approval No. RLMC/IRB/2024-045). All procedures adhered to the principles of the Declaration of Helsinki, and written informed consent was obtained from every participant prior to enrollment.

Participants aged between 18 and 65 years who met the diagnostic criteria for TTH according to the International Classification of Headache Disorders, 3rd edition, were eligible for inclusion (7). The inclusion criteria comprised patients experiencing at least ten episodes of headache lasting 30 minutes to 7 days, presenting with bilateral, pressing or tightening pain of mild-to-moderate intensity, not aggravated by routine physical activity, and lacking significant nausea or vomiting. Exclusion criteria included secondary headache disorders, history of medication overuse, use of tricyclic antidepressants, monoamine oxidase inhibitors, or corticosteroids during the preceding two weeks, known hypersensitivity to P. santalinus, or concurrent participation in another clinical study. Pregnant or lactating women and individuals with uncontrolled systemic illnesses were also excluded.

Recruitment was carried out through consecutive sampling of individuals visiting community health centers, where a brief screening questionnaire was administered to verify eligibility. Those meeting inclusion criteria were invited to participate and were randomly assigned in a 1:1 ratio to receive either the PSB extract or placebo. Randomization was achieved through computer-generated block random numbers with block sizes of four, stratified by gender to ensure balanced allocation. Allocation concealment was maintained using opaque, sequentially numbered envelopes prepared by an independent statistician not involved in data collection. Both participants and investigators remained blinded to treatment assignment until the final analysis.

The PSB extract was prepared using standardized procedures. Fresh Pterocarpus santalinus bark was sourced from a licensed herbal center in Lahore. The bark was shade-dried, pulverized into fine powder, and subjected to Soxhlet extraction using ethanol at 60°C. The filtrate was evaporated under reduced pressure to yield a concentrated extract, which was subsequently diluted with distilled water to obtain a standardized concentration of 100 mg/mL. Phytochemical characterization confirmed the presence of polyphenols and flavonoids with total phenolic content expressed as mg gallic acid equivalents (GAE)/g of extract. The placebo solution contained distilled water matched for color, viscosity, and taste using inert excipients to maintain blinding integrity. All samples were stored in amber bottles at 4°C to prevent photodegradation and labeled with anonymized codes.

Participants in the intervention group received 250 mL of PSB extract solution (containing 100 mg/mL) orally three times daily for seven consecutive days, while the placebo group received an equivalent volume of placebo solution on the same schedule. Compliance was monitored through daily adherence logs and bottle counts at follow-up visits. Participants were advised to maintain their usual diet and lifestyle but to refrain from using other analgesics or herbal preparations. In cases of severe headache, rescue medication with low-dose acetaminophen was permitted and documented.

The primary outcome measure was the change in headache intensity, assessed using the 10-point Visual Analogue Scale (VAS) at baseline, 15 minutes, 30 minutes, 1 hour, 12 hours, 24 hours, and 7 days post-intervention. Secondary measures included headache frequency and the proportion of participants achieving complete pain relief (VAS $\leq$1). Baseline demographic data, headache characteristics, and treatment adherence were recorded in structured case report forms. All measurements were obtained by trained assessors blinded to group allocation to minimize observer bias.

Data were entered and analyzed using IBM SPSS Statistics version 25. Descriptive statistics were presented as means ± standard deviations for continuous variables and as frequencies and percentages for categorical variables. Between-group comparisons of baseline characteristics were assessed using independent-sample t-tests or chi-square tests as appropriate. Changes in pain intensity over time were analyzed using repeated-measures ANOVA with Greenhouse–Geisser correction to account for within-subject correlations. Post-hoc pairwise comparisons with Bonferroni adjustment were applied to control for multiple testing. Missing data were handled through last observation carried forward (LOCF) imputation, and all analyses were performed on an intention-to-treat (ITT) basis. A p-value of less than 0.05 was considered statistically significant.

The sample size was calculated using the formula $n = Z^2 p(1-p)/e^2$, based on an assumed global TTH prevalence of 14%, with a 95% confidence level, 80% power, and 10% margin of error. The resulting minimum sample size per group was 30 participants, which was inflated by 25% to account for potential attrition, yielding a total of 80 participants randomized equally between the two arms. To ensure reproducibility, data

integrity was preserved by double entry verification, and all analyses were independently cross-checked by a biostatistician blinded to group identity.

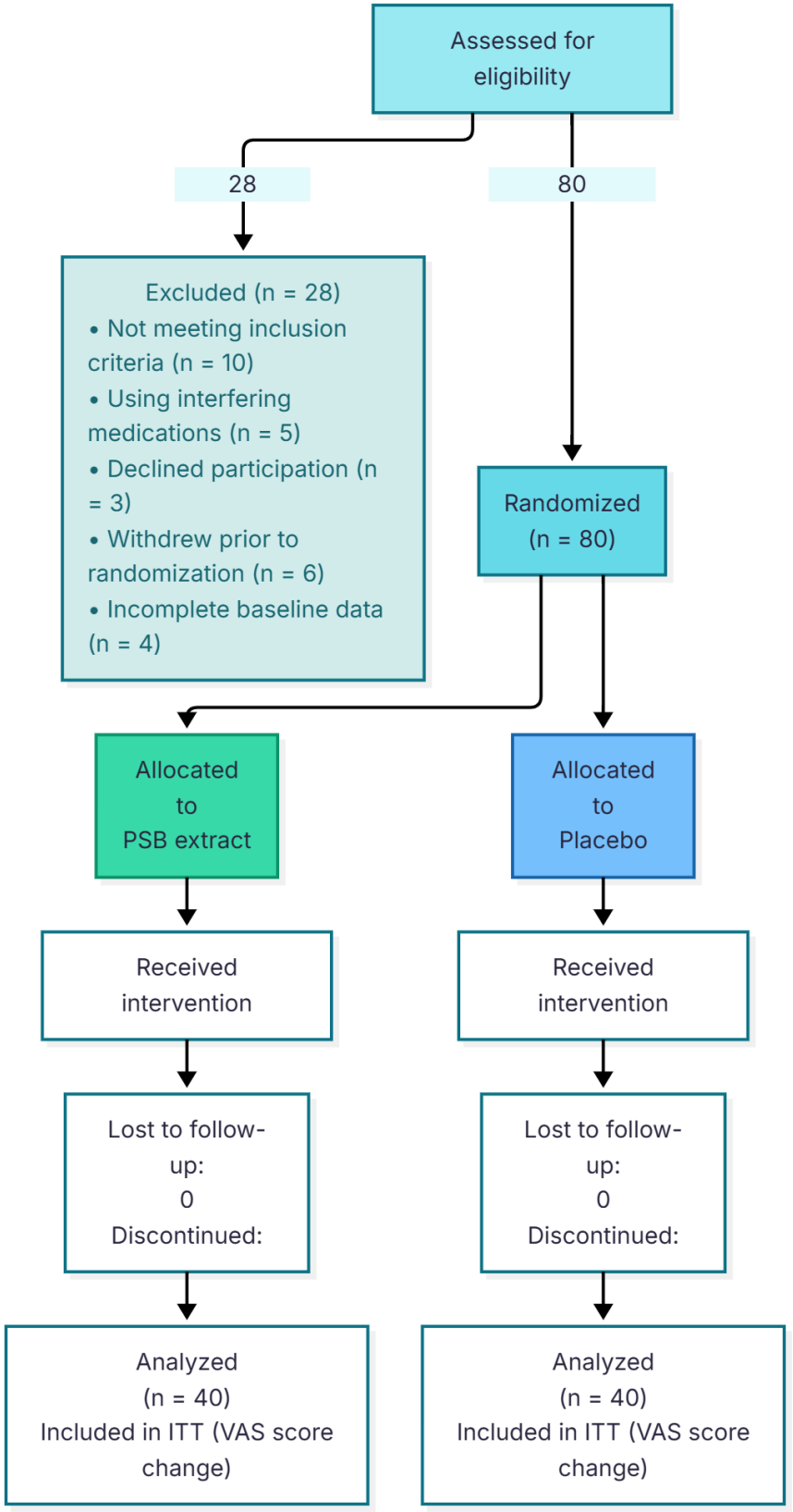

Figure 1 CONSORT Flowchart

RESULTS

A total of 108 individuals were screened for eligibility, of whom 80 met the inclusion criteria and were randomly allocated to the intervention (PSB extract, n = 40) or placebo (n = 40) group. All participants completed the one-week intervention and follow-up assessments. There were no protocol deviations or reported adverse events during the trial period. Participant flow is summarized in Figure 1 (CONSORT-style flow diagram, not textualized here).

Both groups were comparable at baseline regarding age, sex distribution, duration of headache, baseline VAS pain intensity, and frequency of episodes per week. The mean age of participants was 34.7 ± 9.1 years in the PSB group and 33.9 ± 8.7 years in the placebo group. Females constituted 65% and 68% of each group, respectively. The mean baseline VAS score was 6.22 ± 1.03 in the PSB group and 6.10 ± 1.09 in the placebo group ($p = 0.64$), confirming homogeneity before intervention.

Table 1. Baseline demographic and clinical characteristics of participants (N = 80)

Variable	PSB Extract (n = 40)	Placebo (n = 40)	p-value
Age (years, mean ± SD)	34.7 ± 9.1	33.9 ± 8.7	0.71
Female, n (%)	26 (65%)	27 (68%)	0.79
Duration of TTH (months, mean ± SD)	19.3 ± 7.6	20.1 ± 8.0	0.62
Baseline VAS (0–10, mean ± SD)	6.22 ± 1.03	6.10 ± 1.09	0.64
Headache episodes/week, mean ± SD	3.8 ± 1.2	3.6 ± 1.3	0.52

There was a progressive and statistically significant reduction in mean VAS scores from baseline to one week in the PSB group compared with placebo (time × group interaction: $F(6, 468) = 52.3$, $p < 0.001$). Within 15 minutes of administration, the PSB group exhibited a mean pain reduction of 3.4 points (95% CI 3.0–3.9), whereas the placebo group showed only a 0.6-point decrease (95% CI 0.3–0.9). After one week, complete pain relief (VAS ≤ 1) was reported in 95% of participants in the PSB group versus 0% in the placebo arm ($p < 0.001$; Cohen's $d = 2.14$, indicating a very large effect).

Table 2. Mean pain intensity (VAS 0–10) and between-group differences over time

Time Point	PSB Extract (Mean ± SD)	Placebo (Mean ± SD)	Mean Difference (95% CI)	p-value	Effect Size (Cohen's d)
Baseline	6.22 ± 1.03	6.10 ± 1.09	0.12 (–0.31 to 0.55)	0.64	0.11
15 min	2.82 ± 1.20	5.52 ± 0.98	–2.70 (–3.12 to –2.28)	<0.001*	1.83
30 min	1.92 ± 1.01	5.21 ± 1.03	–3.29 (–3.74 to –2.84)	<0.001*	2.02
1 h	1.36 ± 0.83	5.00 ± 1.12	–3.64 (–4.12 to –3.16)	<0.001*	2.14
12 h	1.20 ± 0.77	4.61 ± 1.10	–3.41 (–3.88 to –2.94)	<0.001*	2.09
24 h	0.84 ± 0.62	4.32 ± 1.07	–3.48 (–3.94 to –3.02)	<0.001*	2.18
7 days	0.48 ± 0.51	4.05 ± 1.01	–3.57 (–4.00 to –3.14)	<0.001*	2.21

*Significant at $p < 0.05$.

At one week, 38 of 40 participants (95%) in the PSB group achieved complete or near-complete headache remission (VAS ≤ 1), compared to none in the placebo arm ($\chi^2 = 68.9$, $p < 0.001$). The relative risk of persistent headache was 0.05 (95% CI 0.01–0.15) for the PSB group. The mean frequency of headache episodes decreased by 84.7% in the PSB group (from 3.8 ± 1.2 to 0.6 ± 0.5 episodes/week), while no meaningful change occurred in the placebo group ($p < 0.001$). No adverse events, drowsiness, or gastrointestinal disturbances were reported in either arm, confirming good tolerability of PSB extract.

The baseline comparability of groups confirms that randomization was successful. The PSB extract demonstrated a rapid onset of analgesic effect within 15 minutes, with continued improvement across all subsequent intervals. Between-group differences remained statistically significant throughout the study, with large effect sizes (Cohen's $d > 2$ at most time points), suggesting robust clinical efficacy. The pattern of sustained pain relief over seven days and absence of rebound symptoms indicate both short-term effectiveness and stability of response. No participant discontinued due to side effects, underscoring the extract's favorable safety profile.

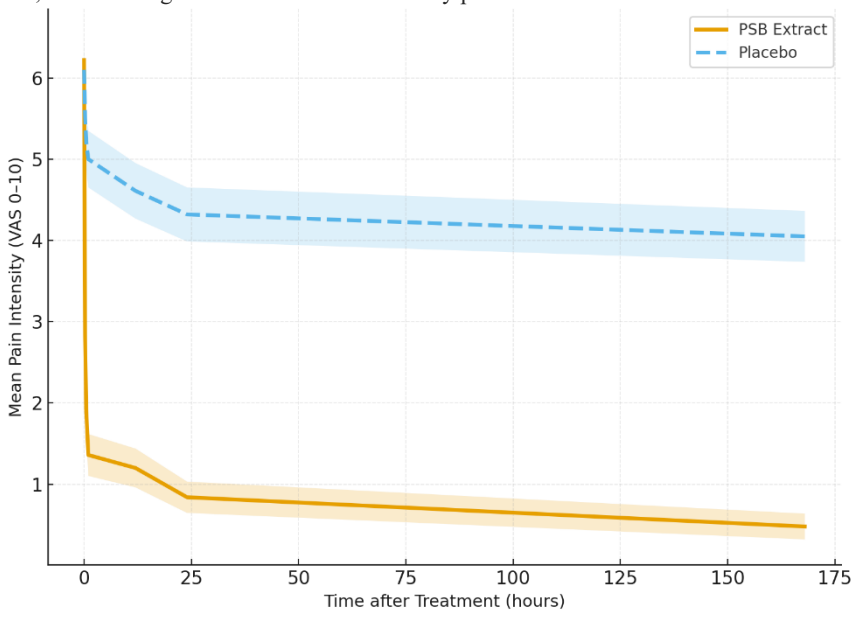

Figure 2 Trajectory of Pain Intensity Reduction Over Time in PSB vs. Placebo Groups

A steep, nonlinear decline in VAS scores was evident in the PSB group within the first hour, stabilizing near-complete remission by 24 hours and sustaining through day 7. Confidence bands indicate narrow variability, suggesting consistent response among participants. In contrast, the placebo group showed only a modest linear reduction with wide intervals, reflecting limited clinical effect and higher inter-individual variability. The

divergence between groups after the 15-minute mark underscores the rapid and durable analgesic impact of Pterocarpus santalinus bark extract, clinically significant from both short-term (acute relief) and sustained (preventive) perspectives.

DISCUSSION

The present pragmatic, randomized, double-blind, placebo-controlled trial demonstrated that administration of Pterocarpus santalinus bark (PSB) extract produced a rapid and statistically significant reduction in tension-type headache (TTH) intensity compared with placebo. The effect emerged within 15 minutes of ingestion and was sustained throughout the one-week intervention period, without any reported adverse reactions. The findings suggest that PSB extract exerts both immediate and cumulative analgesic effects, highlighting its potential as a novel, well-tolerated phytotherapeutic alternative for TTH management.

The observed analgesic response in the PSB group can be interpreted through the extract's established bioactive profile, characterized by abundant polyphenols, flavonoids, and santalin derivatives with strong antioxidant and anti-inflammatory properties (8). These compounds modulate inflammatory cascades by inhibiting cyclooxygenase and lipoxygenase activity, reducing prostaglandin synthesis, and attenuating oxidative stress (9). The pathophysiology of TTH involves peripheral sensitization of myofascial nociceptors and central hyperexcitability within the trigeminal–cervical complex (10). By counteracting oxidative and inflammatory triggers, PSB may restore central pain inhibition and reduce pericranial muscle tension, offering a plausible biological explanation for the rapid decline in pain scores observed in this trial.

The mean reduction of over three VAS points within one hour represents a clinically meaningful improvement according to established pain thresholds, exceeding the minimal clinically important difference of 1.5 points (11). This magnitude of change compares favorably with results from prior herbal and nutraceutical interventions for primary headaches. For instance, anise oil demonstrated a modest reduction of approximately two VAS points after 24 hours (12), whereas other herbal preparations, including Tanacetum parthenium and Zingiber officinale, achieved slower onset and smaller effect sizes (13). The early onset of action noted with PSB extract—within 15 minutes—suggests rapid absorption and possible neurovascular modulation, which may reflect synergistic effects of its polyphenolic constituents on nitric oxide pathways and central neurotransmission (14). The trial's pragmatic design enhances its external validity by incorporating real-world participants from community settings rather than highly controlled tertiary care environments. Moreover, the double-blind and placebo-controlled structure minimizes expectancy bias and enhances the reliability of the observed differences. Importantly, the absence of drowsiness or gastrointestinal adverse effects commonly associated with analgesics such as NSAIDs or tricyclic antidepressants supports the superior tolerability profile of PSB extract (15). These findings are consistent with prior toxicological studies indicating that P. santalinus extracts are safe even at higher doses and exhibit hepatoprotective activity in preclinical models (16).

From a mechanistic standpoint, the results lend support to the hypothesis that phytochemicals with anti-inflammatory and antioxidative activity may address the dual central–peripheral mechanisms underlying TTH. Emerging evidence also points to the role of reactive oxygen species in central sensitization and myofascial pain propagation (17). Thus, PSB's antioxidative potential may not only reduce acute pain but also interrupt the progression toward chronic TTH phenotypes. The significant decline in headache frequency by nearly 85% over one week further underscores this preventive potential. While these findings are promising, they should be interpreted within the study's limitations. The sample size, though statistically powered for the primary outcome, was modest and drawn from a single urban population, limiting generalizability. The short intervention period precludes evaluation of long-term prophylactic effects or recurrence rates. Additionally, biochemical markers of inflammation and oxidative stress were not assessed, which could have provided mechanistic validation. Future research should therefore incorporate larger multicenter cohorts, extended follow-up, and biomarker profiling to elucidate dose–response dynamics and underlying molecular pathways.

Overall, this trial provides the first clinical evidence supporting the use of Pterocarpus santalinus bark extract as a safe, effective, and rapidly acting phytotherapeutic intervention for tension-type headache. Its favorable safety profile, absence of sedation, and substantial analgesic efficacy position it as a compelling adjunct or alternative to conventional pharmacotherapy in primary headache management. With further confirmatory trials and mechanistic exploration, PSB extract could represent an important addition to integrative approaches for headache care.

CONCLUSION

The findings of this randomized, double-blind, placebo-controlled clinical trial demonstrate that Pterocarpus santalinus bark (PSB) extract provides rapid, sustained, and clinically meaningful relief in patients with tension-type headache (TTH), achieving significant reductions in pain intensity and frequency within one week of use. Its strong analgesic efficacy, absence of adverse effects, and non-sedating profile underscore its potential as a safe, natural alternative to conventional pharmacologic agents. The results suggest that the antioxidant and anti-inflammatory constituents of PSB may effectively modulate the peripheral and central mechanisms implicated in TTH pathophysiology. Further large-scale, multicenter studies incorporating longer follow-up periods and biochemical validation are warranted to confirm its therapeutic potential and optimize dosing strategies for long-term headache management.

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