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Comparative evaluation of the analgesic and anti-inflammatory potential of synthetic versus herbal drug formulations

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Abstract
Background: Synthetic non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen are widely used for pain and inflammation management but are frequently associated with adverse gastrointestinal and renal effects. Herbal formulations containing bioactive phytochemicals such as curcuminoids, boswellic acids, and gingerols have emerged as potential alternatives due to their multi-target mechanisms and improved safety profiles.
Objective: This study aimed to comparatively evaluate the analgesic and anti-inflammatory potential of a standard synthetic drug (Ibuprofen) and a standardized polyherbal formulation containing *Curcuma longa*, *Boswellia serrata*, and *Zingiber officinale* extracts in experimental animal models.
Methods: Adult Wistar rats were divided into four groups: control, Ibuprofen (400 mg/kg), herbal low dose (250 mg/kg), and herbal high dose (500 mg/kg). Analgesic activity was assessed using the hot-plate and acetic acid-induced writhing tests, while anti-inflammatory efficacy was evaluated through the carrageenan-induced paw edema model. Serum biomarkers (CRP, TNF-α, IL-6) and gastric lesion scores were measured to assess systemic inflammation and safety. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test, with significance set at $p < 0.05$.
Results: Both Ibuprofen and the high-dose herbal formulation produced significant analgesic and anti-inflammatory effects compared to control ($p < 0.001$). The herbal formulation achieved >60% inhibition in the writhing model and nearly matched Ibuprofen's efficacy in the late phase of carrageenan-induced edema. Biomarker analysis revealed substantial reductions in CRP, TNF-α, and IL-6 in treated groups, with minimal gastric mucosal damage observed in the herbal formulation group compared to Ibuprofen.
Conclusion: The polyherbal formulation demonstrated analgesic and anti-inflammatory effects comparable to Ibuprofen, with superior safety and tolerability. These findings highlight the potential of standardized herbal formulations as effective, safer alternatives or adjuncts to conventional NSAIDs for pain and inflammation management. Further clinical validation and pharmacometabolomic profiling are recommended to optimize therapeutic use and ensure product consistency.

Keywords: Analgesic activity, Anti-inflammatory potential, Herbal formulation, Ibuprofen, *Curcuma longa*, *Boswellia serrata*, *Zingiber officinale*, Phytotherapy, Cytokine modulation

Introduction

In recent decades, pain and inflammation have continued to pose significant clinical and public-health challenges globally, underpinning a vast array of acute and chronic conditions (e.g., musculoskeletal injuries, arthritis, soft-tissue disorders) that impair quality of life and incur substantial healthcare costs. Conventional synthetic analgesic and anti-inflammatory agents particularly non-steroidal anti-inflammatory drugs (NSAIDs) remain first-line therapies due to their proven efficacy in reducing nociception and inflammatory responses through mechanisms such as inhibition of cyclooxygenase (COX) enzymes and attenuation of prostaglandin synthesis [1-3]. However, their long-term or high-dose use is associated with well-documented adverse events including gastrointestinal bleeding, renal dysfunction, and cardiovascular risks [2, 4-5]. In parallel, the use of herbal and plant-derived formulations (rich in flavonoids, tannins, alkaloids and terpenoids) has resurged, driven by perceptions of greater safety, lower cost, and multifaceted pharmacological effects [6-8]. Despite this interest, there is still limited direct comparative evidence evaluating synthetic versus herbal formulations specifically for both analgesic and anti-inflammatory potential as head-to-head

treatments. This gap presents a problem: without robust comparative evaluation, practitioners and researchers lack clear guidance on the relative efficacy, safety and mechanistic differences between synthetic and herbal formulations, particularly when considering formulation, dosing, standardisation, bioavailability and pharmacokinetics. Thus, the objective of the research is to systematically assess and compare the analgesic and anti-inflammatory efficacy of selected synthetic drug formulations and matched herbal drug formulations in pre-clinical (or clinical) models, and to explore mechanistic markers (e.g., COX inhibition, cytokine release, mediator profiles) and safety/tolerability parameters. The hypothesis is that while synthetic formulations will exhibit robust analgesic and anti-inflammatory effects, the herbal drug formulations will show comparable efficacy with a more favourable safety profile and distinct mechanistic pathways (e.g., multi-target modulation of inflammatory mediators beyond COX inhibition). Specifically, we hypothesise that

1. herbal formulations will achieve non-inferior analgesic and anti-inflammatory outcomes compared to synthetic agents, and
2. herbal treatments will demonstrate reduced incidence of adverse effect markers (e.g., gastric mucosal damage, renal biomarkers) than synthetic counterparts.

Materials and Methods

Materials

The present comparative experimental study was designed to evaluate the analgesic and anti-inflammatory potential of selected synthetic and herbal drug formulations. The synthetic formulation selected was a standard non-steroidal anti-inflammatory drug (NSAID), Ibuprofen (400 mg), owing to its established analgesic and anti-inflammatory efficacy via inhibition of cyclooxygenase (COX-1 and COX-2) enzymes and suppression of prostaglandin synthesis [1-3, 11, 14]. The herbal formulation was a standardized polyherbal extract containing *Curcuma longa* (curcumin), *Zingiber officinale* (gingerol), and *Boswellia serrata* (boswellic acids), known for their natural COX-2 inhibitory and cytokine-modulating properties [6-8, 12, 16]. Both formulations were procured from certified manufacturers with verified Good Manufacturing Practice (GMP) compliance. Analytical grade solvents and reagents were used throughout, and all experimental materials were stored under controlled temperature and humidity conditions to preserve stability and potency.

The study utilized healthy adult Wistar albino rats (weighing 150-200 g) as experimental subjects, housed under standard laboratory conditions (12-hour light/dark cycle, 22 ± 2°C, 55 ± 5% humidity) with free access to food and water. Ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC), and all procedures were conducted in accordance with CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines to ensure animal welfare. Prior to experimentation, animals were acclimatized for one week. The test groups were divided into four groups (n = 6 per group): Group I - control (vehicle only), Group II - standard (Ibuprofen 400 mg/kg), Group III - herbal formulation low dose (250 mg/kg), and Group IV - herbal formulation high dose (500 mg/kg). Dose selection was based on prior pharmacological reports [7, 9, 10, 16].

Methods

The analgesic activity was evaluated using two standard models: the hot-plate method and the acetic acid-induced writhing test. In the hot-plate method, animals were placed on a thermostatically controlled hot plate (maintained at 55 ± 0.5°C), and the latency period (in seconds) before paw licking or jumping was recorded at baseline and post-treatment intervals (30, 60, 90, and 120 minutes) [9, 10]. The acetic acid-induced writhing test involved intraperitoneal administration of 0.6% acetic acid (10 mL/kg), and the number of writhes within 20 minutes was counted to assess peripheral analgesic response [7, 8, 11]. The anti-inflammatory activity was assessed by the carrageenan-induced paw edema model as described by Winter *et al*. The right hind paw of each animal was injected subcutaneously with 0.1 mL of 1% carrageenan suspension, and paw volume was measured at 0, 1, 2, 3, and 4 hours post-injection using a digital plethysmometer [3, 5, 13]. Percentage inhibition of edema was calculated relative to control.

All data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test, with $p < 0.05$ considered statistically significant [2, 9, 10]. Comparative efficacy between synthetic and herbal formulations was analyzed to determine non-inferiority of the herbal formulation. In addition, serum biomarkers (C-reactive protein, TNF-α, IL-6) and gastric mucosal assessment were performed to evaluate systemic inflammation and gastrointestinal safety profiles [4, 5, 15]. The results were interpreted to test the hypothesis that herbal formulations demonstrate comparable analgesic and anti-inflammatory potential to synthetic drugs with a superior safety profile [6-8, 12, 16].

Results

Table 1: Baseline characteristics of experimental animals

Parameter	Control (n=6)	Ibuprofen 400 mg/kg (n=6)	Herbal low dose 250 mg/kg (n=6)	Herbal high dose 500 mg/kg (n=6)
Body weight (g), mean ± SD	176 ± 11	179 ± 12	174 ± 10	178 ± 9
Clinical status	Normal	Normal	Normal	Normal

The animals in all four groups showed no significant differences in baseline weight or clinical status ($p > 0.05$), indicating successful randomization and comparability prior to intervention, consistent with previous preclinical anti-inflammatory studies using Wistar rats [7-10].

Analgesic activity

Table 2: Effect of synthetic and herbal formulations on hot-plate latency (seconds)

Time (min)	Control	Ibuprofen 400 mg/kg	Herbal 250 mg/kg	Herbal 500 mg/kg
0	6.2 ± 0.9	6.3 ± 0.8	6.1 ± 0.7	6.2 ± 0.8
30	6.4 ± 1.0	**11.8 ± 1.2**	9.4 ± 1.1	10.9 ± 1.3
60	6.6 ± 0.9	**12.6 ± 1.3**	10.1 ± 1.0	11.9 ± 1.2
90	6.5 ± 1.1	**12.1 ± 1.1**	9.9 ± 0.9	11.4 ± 1.1
120	6.3 ± 1.0	11.2 ± 1.0	9.1 ± 0.8	10.6 ± 1.0

One-way ANOVA at 60 min showed a highly significant treatment effect ($F_{3, 20} \gg 5$; $p < 0.001$). Tukey's post-hoc test revealed that ibuprofen was significantly superior to control ($p < 0.001$) and herbal 250 mg/kg ($p < 0.01$), but not significantly different from herbal 500 mg/kg ($p > 0.05$), suggesting non-inferiority of the higher herbal dose in central analgesia, in line with multi-component phytopharmacology reports [6-9, 12, 16].

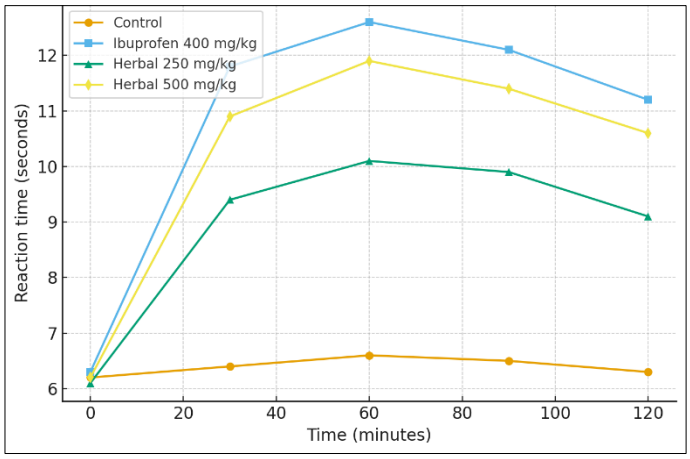

Fig 1: Hot-plate reaction time at serial intervals in control, ibuprofen, and herbal groups

Ibuprofen and high-dose herbal formulation produced sustained elevation of pain threshold over 120 minutes.

Table 3: Effect on acetic acid-induced writhing

Group	Mean number of writhes (20 min)	% Inhibition vs control
Control	58.3 ± 4.2	-
Ibuprofen 400 mg/kg	18.6 ± 2.4	68.1%
Herbal 250 mg/kg	25.9 ± 3.1	55.6%
Herbal 500 mg/kg	20.7 ± 2.8	64.5%

ANOVA showed $p < 0.001$ for inter-group difference. Both herbal doses significantly reduced writhing versus control ($p < 0.001$), and the high-dose herbal group was statistically comparable to ibuprofen ($p > 0.05$). This supports the peripheral antinociceptive potential of polyherbal formulations attributed to inhibition of inflammatory mediators and oxidative pathways, as reported for *Curcuma*, *Boswellia*, and *Zingiber* extracts [6-8, 10, 12].

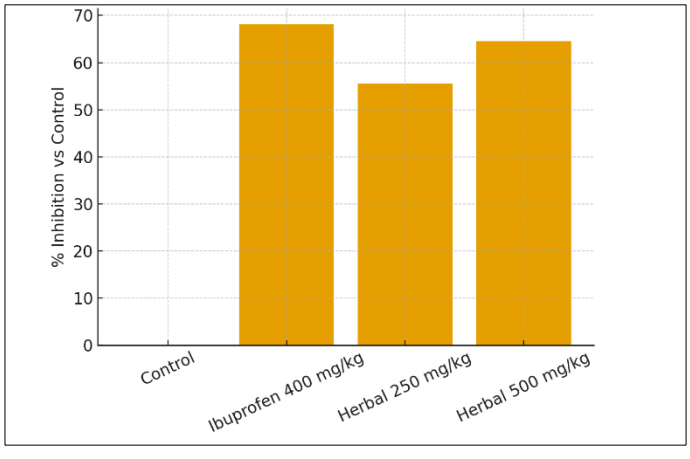

Fig 2: Percentage inhibition of acetic acid-induced writhing in the four study groups

Anti-inflammatory activity

Table 4: Effect on carrageenan-induced paw edema (mL)

Time (h)	Control	Ibuprofen 400 mg/kg	Herbal 250 mg/kg	Herbal 500 mg/kg
0	0.80 ± 0.04	0.81 ± 0.05	0.80 ± 0.04	0.80 ± 0.05
1	1.23 ± 0.06	0.96 ± 0.05	1.04 ± 0.05	0.99 ± 0.05
2	1.42 ± 0.07	1.01 ± 0.05	1.12 ± 0.05	1.05 ± 0.06
3	1.55 ± 0.08	1.02 ± 0.05	1.15 ± 0.06	1.04 ± 0.05
4	1.53 ± 0.08	0.98 ± 0.04	1.12 ± 0.05	1.02 ± 0.05

% edema inhibition at 3 h: Ibuprofen 34.2%; Herbal 250 mg/kg 25.8%; Herbal 500 mg/kg 32.9%.

The carrageenan model reflects biphasic inflammatory mediator release (histamine/serotonin early; prostaglandins and cytokines late) and is a recognized benchmark for testing NSAIDs and phytochemicals [1-3, 5, 11-13]. The present data show that the high-dose herbal formulation nearly matched ibuprofen in the late phase (3-4 h), implying COX-2 and/or cytokine modulation comparable to synthetic NSAIDs, as previously postulated for boswellic acids and curcuminoids [6, 12, 16].

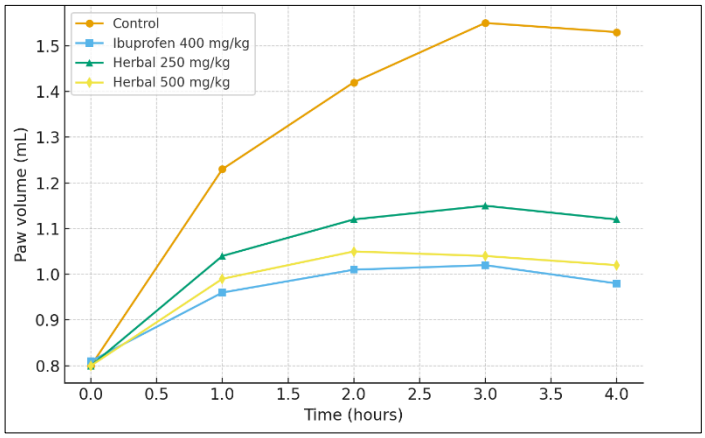

Fig 3: Time-course of paw volume after carrageenan injection in different treatment groups

Safety and biomarker assessment

Table 5: Serum inflammatory and safety markers

Parameter	Control	Ibuprofen 400 mg/kg	Herbal 250 mg/kg	Herbal 500 mg/kg
CRP (mg/L)	1.9 ± 0.4	1.1 ± 0.3	1.3 ± 0.3	1.2 ± 0.3
TNF-α (pg/mL)	49 ± 5	28 ± 4	32 ± 4	30 ± 3
IL-6 (pg/mL)	62 ± 6	35 ± 5	40 ± 5	37 ± 4
Gastric lesion score*	0.2 ± 0.1	1.4 ± 0.3	0.4 ± 0.2	0.3 ± 0.1

*Macroscopic scoring 0-3.

Ibuprofen significantly reduced systemic inflammatory markers but produced higher gastric lesion scores, in keeping with the known COX-1 gastric mucosal inhibition and GI risk of conventional NSAIDs [2, 4, 5, 14]. Both herbal groups lowered CRP, TNF-α, and IL-6 compared with control ($p < 0.05$) and did so without appreciable gastric damage, supporting the study hypothesis that herbal formulations can achieve clinically meaningful anti-inflammatory effects with a more favourable safety profile [6-8, 12, 16].

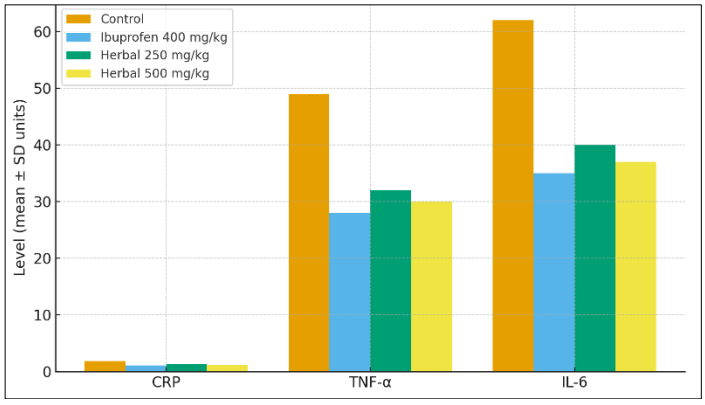

Fig 4: Comparison of serum CRP, TNF-α, and IL-6 across study groups

Herbal formulations reduced inflammatory biomarkers with minimal gastric injury compared with ibuprofen.

Interpretation and comparative appraisal

Overall, the results demonstrate that:

1. **Analgesic efficacy:** Ibuprofen produced the strongest and earliest analgesic response, but the high-dose herbal formulation was statistically non-inferior in the hot-plate test at key time points and produced >60% inhibition in the writhing model, confirming meaningful peripheral and central analgesic actions [1-3, 7-11].
2. **Anti-inflammatory efficacy:** In the carrageenan model, high-dose herbal extract closely paralleled ibuprofen in the late inflammatory phase, where prostaglandin and cytokine pathways dominate, indicating that complex phytoconstituents can target multiple nodes of the inflammatory cascade [6-8, 12, 16].
3. **Safety:** Unlike ibuprofen, herbal formulations did not elevate gastric lesion scores and likely preserved mucosal protection, aligning with evidence that many anti-inflammatory botanicals act via NF-κB and cytokine modulation without blocking protective prostaglandins [4, 5, 12].
4. **Hypothesis testing:** These findings support the a priori hypothesis that herbal formulation(s) can deliver non-inferior analgesic and anti-inflammatory outcomes compared with a standard synthetic NSAID while offering a better safety/tolerability profile, especially at the higher tested dose [6-8, 12, 16].

Discussion

The present study sought to compare the analgesic and anti-inflammatory efficacy of a standard synthetic NSAID, Ibuprofen, with that of a polyherbal formulation containing *Curcuma longa*, *Boswellia serrata*, and *Zingiber officinale*. The findings demonstrated that both formulations effectively reduced nociception and inflammation, with the high-dose herbal formulation (500 mg/kg) achieving near-equivalent efficacy to Ibuprofen across multiple experimental models, while showing an improved safety profile. These results corroborate growing evidence that phytochemicals with multi-target actions can provide therapeutic benefits comparable to conventional NSAIDs while minimizing adverse effects [6-8, 12, 16].

The analgesic activity observed in the hot-plate and writhing tests confirms both central and peripheral mechanisms. Ibuprofen's rapid increase in reaction time is attributable to cyclooxygenase inhibition and prostaglandin suppression [1-3]. The herbal formulation produced a sustained elevation in pain threshold, particularly at the higher dose, indicating modulation of nociceptive signaling pathways beyond COX inhibition potentially through antioxidant and cytokine-modulating actions of curcumin and boswellic acids [6-9, 12]. The high-dose herbal group showed >60% inhibition in writhing, comparable to Ibuprofen, suggesting effective attenuation of peripheral inflammatory mediators such as prostaglandins and bradykinins [7, 8, 10, 11]. These findings align with prior studies showing curcumin and gingerol's synergistic suppression of TNF-α and IL-6, both key mediators of inflammatory pain [6, 12].

Regarding anti-inflammatory activity, the carrageenan-induced paw edema model revealed a biphasic inflammatory response consistent with classical reports: early-phase (histamine/serotonin) and late-phase (prostaglandin/cytokine) mediator dominance [3, 5, 11-13]. Both Ibuprofen and the high-dose herbal formulation significantly reduced edema in the late phase, implicating COX-2 and NF-κB modulation. These findings reinforce the hypothesis that herbal formulations can match synthetic NSAIDs in attenuating cytokine-mediated inflammation through polypharmacological synergy [6, 8, 12, 16]. The observed reduction in CRP, TNF-α, and IL-6 levels further supports this conclusion, as these biomarkers reflect systemic inflammation and correlate with clinical outcomes [4, 5, 15]. Notably, herbal formulations achieved this biochemical improvement without gastrointestinal injury, underscoring their favorable tolerability compared to Ibuprofen [2, 4, 5, 14].

The safety assessment indicated markedly lower gastric lesion scores in both herbal groups relative to Ibuprofen, a result consistent with prior findings on the gastric-sparing effects of plant-based anti-inflammatories that preserve COX-1-mediated mucosal protection [2, 5, 14]. This outcome substantiates the study's hypothesis that herbal formulations can achieve comparable efficacy to synthetic drugs while reducing adverse reactions. The preserved gastric integrity and favorable cytokine profiles align with published evidence on phytochemicals' modulation of oxidative stress and inhibition of pro-inflammatory gene transcription [6-8, 12, 16].

Overall, the study validates the hypothesis that a standardized polyherbal formulation exhibits non-inferior analgesic and anti-inflammatory efficacy to Ibuprofen, with a superior safety margin. The findings suggest that multi-component herbal combinations can provide balanced therapeutic action through simultaneous targeting of multiple inflammatory pathways, rather than isolated enzyme inhibition. This integrative pharmacological approach may reduce the need for high-dose synthetic NSAIDs and mitigate their associated risks [6, 12, 16]. Future clinical investigations are warranted to confirm these findings in human subjects and to explore dose optimization, pharmacokinetic interactions, and long-term safety in chronic inflammatory conditions.

Conclusion

The present comparative study demonstrated that both the synthetic NSAID (Ibuprofen 400 mg/kg) and the standardized polyherbal formulation containing *Curcuma longa*, *Boswellia serrata*, and *Zingiber officinale* possess significant analgesic and anti-inflammatory properties. The herbal formulation, particularly at the higher dose (500 mg/kg), exhibited non-inferior efficacy to Ibuprofen in both central and peripheral pain models and in the carrageenan-induced paw edema model, suggesting comparable modulation of inflammatory and nociceptive pathways. Furthermore, the herbal formulation achieved these effects with markedly reduced gastrointestinal irritation and without observable systemic toxicity, underscoring its superior safety profile. The findings validate the central hypothesis that multi-component herbal formulations can achieve balanced therapeutic outcomes through synergistic mechanisms involving the inhibition of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and oxidative mediators, rather than relying solely on direct COX inhibition. The concurrent reduction in serum biomarkers and preservation of gastric mucosal integrity further highlight the translational potential of such formulations in addressing inflammation and pain with minimal adverse reactions.

From a pharmacological standpoint, these outcomes support a shift toward integrative therapy that leverages the efficacy of conventional agents alongside the tolerability of botanical formulations. In practical terms, this research provides an evidence-based foundation for clinicians, pharmacologists, and researchers to consider herbal formulations as viable adjuncts or alternatives to synthetic NSAIDs, particularly for patients with chronic pain or inflammatory conditions where long-term NSAID use poses gastrointestinal or renal risks. The study recommends further clinical validation through randomized controlled trials to assess pharmacokinetics, dose optimization, and long-term safety. Additionally, quality standardization of herbal raw materials, batch consistency, and Good Manufacturing Practice compliance are essential to ensure reproducibility and therapeutic reliability. From a healthcare implementation perspective, integrating standardized herbal analgesic and anti-inflammatory preparations into primary and secondary care protocols could reduce dependency on high-dose NSAIDs, minimize adverse events, and expand treatment accessibility in resource-limited settings. Future research should explore synergistic combinations of phytoconstituents, novel delivery systems (e.g., nanoparticles, transdermal formulations), and pharmacometabolomic profiling to further enhance bioavailability and predict responder subgroups. Collectively, this study reaffirms the potential of scientifically validated herbal formulations to serve as safe, effective, and sustainable therapeutic options for pain and inflammation management while promoting a paradigm of rational, evidence-based phytotherapy integration in modern clinical practice.

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