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Overcoming the Curcumin Absorption Barrier: A Novel Oral Formula for Synergistic Cytokine Inhibition and Skin Barrier Repair

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Abstract: Curcumin demonstrates potent multi-target anti-inflammatory and antioxidant activities but is severely limited by poor water solubility, rapid phase II metabolism, and low oral bioavailability. Herein, a dual delivery system integrating supramolecular cocrystal and self-emulsifying water–oil dual solubilization technologies was developed, combined with exogenous tetrahydrocurcumin (THC) supplementation. The formulation achieved 98.02% relative bioavailability and >297-fold higher systemic exposure of active constituents than conventional curcumin. Further synergized with fish oil, astaxanthin, nicotinamide, vitamin B6, and zinc, the composition established an integrated network targeting anti-inflammation, skin barrier repair, and pigment regulation. A 12-week randomized, double-blind, placebo-controlled trial in 40 subjects with mild-to-moderate acne showed that serum IL-6 was reduced by 48.09%, acne lesion count by 52.41%, accompanied by improved sebum secretion, skin hydration, and melanin index. This delivery strategy significantly enhances the bioefficacy of poorly bioavailable natural products, offering a safe and effective systemic intervention for inflammatory skin diseases.

1. Introduction

Acne is a chronic inflammatory skin disease driven by the combined effects of excessive sebum secretion, microbial dysbiosis, and systemic inflammatory cascades. Clinical studies have confirmed that inflammatory response is the core initiating factor throughout the course of the disease [1,2]. Overexpression of pro-inflammatory factors such as IL-6, IL-1 and TNF-α not only induces clinical symptoms such as redness and pustules, but also continuously destroys dermal collagen after inflammation subsides, leading to persistent post-inflammatory hyperpigmentation (PIH) or scar formation [3], which seriously affects patients' skin health and quality of life.

Curcumin possesses multi-target anti-inflammatory and strong antioxidant biological activities, showing great application potential in the intervention of skin inflammation [4]. However, ordinary curcumin has strong hydrophobicity, poor intestinal absorption, significant hepatic first-pass effect, and rapid metabolic inactivation in vivo, resulting in extremely low bioavailability, which

constitutes the core bottleneck for its clinical translation [5,6]. Although existing technologies have attempted to improve utilization through delivery methods such as liposomes, nanomicelles, or compounding with piperine [7-9], they often overlook the independent role and advantages of tetrahydrocurcumin (THC), the core active metabolite. Studies have shown that THC has higher chemical stability, better water solubility, and stronger anti-inflammatory and antioxidant activities, serving as the key material basis for curcumin to exert its in vivo efficacy [10-12].

To break through the pharmacokinetic limitations of curcuminoids, this study developed a novel oral high-absorption nutritional composition. Through the combined application of supramolecular co-crystal technology and self-emulsifying water-oil dual-phase fusion technology, a breakthrough equivalent bioavailability of 98.02% of the core active ingredients was achieved. Combined with the synergistic formulation of fish oil, astaxanthin, nicotinamide and zinc, a full-chain intervention network of "anti-inflammation-repair-whitening" was constructed [13,14]. This study further evaluated the efficacy of the composition through a 12-week human clinical study, and the results confirmed its excellent efficacy in reducing systemic inflammation and improving acne lesions.

2. Materials and Methods

2.1 Experimental Materials

The core matrix of this study consisted of curcumin and THC. The anti-acne nutritional supplement used in the experiment was in soft capsule form to ensure optimal stability and delivery effect. Each capsule contained 500 mg of active curcuminoids (consisting of curcumin and THC), 100 mg of fish oil, 50 mg of nicotinamide, 2 mg of vitamin B6 and 2 mg of zinc. The composition was prepared via supramolecular co-crystal technology and water-oil dual-phase fusion technology. All experimental materials involved in this study, including curcumin, THC and the finished composition, were provided by GPO LIEF PTE. LTD.

2.2 Evaluation of Pharmacokinetics and Equivalent Bioavailability

2.2.1 Determination of Basic Intestinal Absorption Rate (c)

SPF-grade C57BL/6 mice (n=10) were selected. Ordinary curcumin was administered by gavage at a dose of 500.0 mg/kg. Mice were sacrificed 3 hours after administration, and the contents of the stomach and the entire small intestine were completely collected. Residual free curcumin was fully extracted with ethyl acetate, and its content was detected by high performance liquid chromatography (HPLC) to determine the amount of unabsorbed active ingredients. The basic absorption rate (c %) was calculated using the following formula:

$$c = \frac{\text{Oral Curcumin Dose-Residual Curcumin Content}}{\text{Oral Curcumin Dose}} \times 100$$

2.2.2 Evaluation of Equivalent Bioavailability (F)

Equivalent bioavailability (F) was used in this study to quantify the total systemic exposure of the active metabolite (THC) in the oral composition relative to the ordinary curcumin control group.

To evaluate this indicator, 20 mice were randomly divided into two experimental groups (n=10):Group A (Control group): Administered with ordinary curcumin.Group B (Experimental group): Administered with the optimized composition treated by dual delivery technology (curcumin to THC ratio = 2:1).

All groups received a single oral gavage administration (curcumin equivalent dose 500.0 mg/kg).

Blood samples were collected periodically within 24 hours, and plasma THC concentration was detected by LC-MS/MS for calculation. The formula for equivalent bioavailability (F%) is as follows:

$$F=\frac{AUC_{\text{Test}}}{AUC_{\text{Control}}}\times c$$

2.3 Verification of Human Clinical Efficacy

2.3.1 Subject Recruitment and Grouping

A total of 40 healthy Asian female subjects aged 18–35 years with mild to moderate acne were recruited for this clinical study.

Inclusion criteria: Facial acne conforming to Pillsbury grade I–II (mild to moderate); accompanied by excessive sebum secretion, persistent erythema, and post-inflammatory hyperpigmentation tendency; unable to tolerate or unwilling to use conventional drug therapy; voluntarily signed informed consent and able to cooperate with 12 weeks of intervention and follow-up.

Exclusion criteria: Used anti-inflammatory drugs, hormones, or immunosuppressants in the past 4 weeks; oral isotretinoin in the past 3 months; oral antibiotics, contraceptives, or facial medical beauty/surgery in the past 4 weeks; pregnant or lactating women; no other oral or topical anti-acne products were allowed during the trial.

2.3.2 Study Design

This was a randomized, double-blind, placebo-controlled study. After recruitment, subjects were randomly divided into the experimental group (composition soft capsules) (n=20) and the control group (placebo soft capsules with identical appearance) (n=20). Subjects were required to take one soft capsule daily for 12 weeks. Daily diet and routine were kept stable during the trial.

2.3.3 Sample Collection and Detection Indicators

Subjects were required to undergo sampling and detection at Week 0 (baseline), Week 6, and Week 12, respectively:(1) Blood indicators: Venous blood was collected on an empty stomach, left to stand and centrifuged to obtain serum, and serum IL-6 and reactive oxygen species (ROS) levels were detected. (2) Objective skin indicators: Professional dermatologists took facial images under standard light sources to count acne lesions (total number of papules, pustules, and nodules). Skin hydration, melanin index and sebum level were detected by a skin tester simultaneously. (3) Subjective evaluation: The 0–10 Visual Analogue Scale (VAS) was used to record acne improvement score and quality of life improvement score.

2.4 Statistical Analysis

All data were presented as Mean ± SD, and statistical analysis was performed using SPSS 26.0 software.Paired t-test was used for intra-group comparison, independent t-test for inter-group comparison, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Pharmacokinetics and Bioavailability Results

3.1.1 Basic Intestinal Absorption Rate (c)

Preliminary studies confirmed the severe absorption limitation of natural curcumin. After oral gavage of 500.0 mg/kg, analysis of gastrointestinal residual content showed that ordinary curcumin was extremely difficult to be absorbed by intestinal mucosa. The calculated basic absorption rate c was only 0.33%, meaning that more than 99.6% of ordinary curcumin was unabsorbed or rapidly excreted. More than 99.6% of natural curcumin cannot effectively cross the intestinal mucosal barrier into the systemic circulation due to its extremely high hydrophobicity and unstable chemical structure, which constitutes the main bottleneck for the clinical application of curcumin [15].

3.1.2 Evaluation of Equivalent Bioavailability

In pharmacokinetic studies, the core challenge in evaluating curcuminoids lies in their extremely short half-life and rapid metabolic transformation [15]. As the main hydrogenated metabolite of curcumin in vivo, THC exhibits better physicochemical properties and biological activity than the parent curcumin, and part of curcumin is rapidly metabolized to THC after entering the circulatory system [16]. Studies have shown that THC has higher chemical stability and water solubility under physiological pH conditions, and can more effectively cross biological membrane barriers into tissue cells [17,18]. More importantly, THC has been proven to have higher activities than curcumin in scavenging free radicals, inhibiting pro-inflammatory factors and regulating melanin metabolism [10-12].

Therefore, this study calculated the equivalent bioavailability (F) by quantitatively detecting the content of THC in plasma and combining it with the basic intestinal absorption rate (c). This evaluation method can more comprehensively and scientifically measure the actual active output of the oral composition in vivo and the contribution of delivery technology to the overall utilization efficiency of ingredients.

Supramolecular cocrystal technology rearranges curcumin and THC molecules with specific cocrystal formers at the molecular level, breaking the high lattice energy of natural curcumin. This molecular modification alters the physicochemical properties of active ingredients, markedly enhancing their saturation solubility and dissolution rate in intestinal fluid [19].

Water–oil dual solubilization technology enables the formulation to self-emulsify into nano-sized microemulsions upon contact with the aqueous gastrointestinal environment, greatly increasing the contact area between active ingredients and intestinal epithelial cells. By mimicking the lipid absorption pathway, this technology significantly improves the permeability of ingredients across the small intestinal mucosa, thereby partially avoiding hepatic first-pass metabolism [7,20].

Exogenous THC supplementation bypasses the in vivo reductive metabolism of curcumin. THC becomes immediately active after absorption and acts synergistically with delivery systems to further boost the utilization of active components.

These combined effects address the three major limitations of curcumin: poor solubility, low permeability, and extensive first-pass metabolism.

The experimental data (Table 1) showed that the experimental group exhibited excellent absorption characteristics, with an equivalent bioavailability of 98.02%. This means that through supramolecular co-crystal and water-oil dual-phase fusion technologies, this study successfully increased the in vivo utilization efficiency of active ingredients by approximately 297 times.

Table 1 Pharmacokinetic parameters and relative bioavailability of curcuminoids in mice

Group	$AUC_{0-24}h$ (μg·h/L)	Equivalent Bioavailability (F)
Control group	526.18 ± 48.32	-
Experimental group	156,291.56 ± 12,456.78	98.02%

3.2 Human Efficacy Test Results

3.2.1 Analysis of Inflammatory and Oxidative Factors

During the 12-week clinical intervention, the systemic inflammation and oxidative stress levels of subjects in the experimental group showed a significant gradual decrease. Biochemical test results (Table 2) showed that the concentration of the core pro-inflammatory cytokine IL-6 in the serum of the experimental group steadily decreased from the baseline of 46.58 ± 5.12 pg/mL to 35.42 ± 4.05 pg/mL at Week 6 and 24.18 ± 3.16 pg/mL at the end of Week 12, with a total decrease of 48.09%. Meanwhile, the ROS index reflecting the body's oxidative stress status also showed a similar improvement trend, with a 32.78% decrease in the experimental group at Week 12 compared with the baseline. In contrast, the placebo group remained relatively stable during the trial, and the differences between the two groups at Week 6 and Week 12 were statistically significant ($P < 0.05$).

Table 2 Changes in serum inflammatory and oxidative stress indicators

Group/Time	IL−6 (pg/mL)	ROS (U/mL)
Experimental Group		
Week 0 (Baseline)	46.58 ± 5.12	185.60 ± 20.34
Week 6	35.42 ± 4.05	156.24 ± 17.15
Week 12	24.18 ± 3.16	124.76 ± 14.82
Placebo Group		
Week 0 (Baseline)	47.12 ± 5.45	184.25 ± 21.08
Week 6	44.30 ± 5.30	183.05 ± 20.62
Week 12	40.85 ± 5.26	181.50 ± 20.15

3.2.2 Quantitative Evaluation of Skin Detection Indicators

Objective instrument test results confirmed that oral administration of this composition had a definite repair effect on facial acne lesions and physiological parameters. Statistics of inflammatory lesion counts by professional dermatologists (Table 3) showed that the average number of acne in subjects of the experimental group was significantly reduced from 25.30 at baseline to 12.04 at Week 12, with a reduction rate of 52.41%. In terms of skin barrier and metabolic regulation, the experimental group showed robust improvements: sebum level decreased from 216.5±25.4 μg/cm² to 189.4 ± 21.2 μg/cm² within 12 weeks; skin hydration increased from 30.8 ±4.1 AU to 36.2 ± 3.6 AU. In addition, the melanin index (MI) reflecting pigmentation showed an 11.37% decrease within 12 weeks. All indicators of the placebo group only showed a slight improvement trend at Week 12, but the overall physiological parameters remained at a high level.

Table 3 Changes in objective skin physiological indicators

Group/Time	Acne Count	Skin Hydration (AU)	Melanin Index (MI)	Sebum Level (μg/cm²)
Experimental Group				
Week 0 (Baseline)	25.30 ± 4.60	30.8 ± 4.1	164.5 ± 17.2	216.5 ± 25.4
Week 6	18.50 ± 3.20	33.5 ± 3.8	154.2 ± 15.6	198.6 ± 22.8
Week 12	12.04 ± 2.45	36.2 ± 3.6	145.8 ± 13.5	189.4 ± 21.2
Placebo Group				
Week 0 (Baseline)	24.95 ± 4.82	30.5 ± 4.3	165.2 ± 16.8	218.2 ± 27.4
Week 6	24.10 ± 4.55	30.7 ± 4.0	164.8 ± 16.2	217.1 ± 26.5
Week 12	23.40 ± 4.40	30.9 ± 4.1	164.2 ± 15.9	216.3 ± 25.8

3.2.3 Subjective Evaluation of Subjects

Subjects' subjective feelings on the intervention effect were highly consistent with the objective skin detection indicators. As shown in Table 4, according to the 0-10 VAS score, the "acne improvement degree" score of subjects in the experimental group increased from 2.52 ± 1.25 at Week 6 to 5.35 ± 1.42 at Week 12, showing high satisfaction with the speed of lesion resolution. In addition, the self-rated quality of life improvement score of subjects in the experimental group increased from 3.54 ± 0.86 at baseline (indicating anxiety due to skin problems) to 7.24 ± 0.95 at Week 12, showing a significant enhancement in social confidence. The subjective scores of subjects in the placebo group changed very little during the trial, and both the improvement score and quality of life score at Week 12 were at a low level, proving the positive significance of the experimental intervention in improving mental health and quality of life.

Table 4 Subjective score results of subjects

Group/Time	Acne Improvement Score (0-10)	Quality of Life Improvement Score (0-10)
Experimental Group		
Week 0 (Baseline)	0.00 ± 0.00	3.54 ± 0.86
Week 6	2.52 ± 1.25	5.62 ± 1.14
Week 12	5.35 ± 1.42	7.24 ± 0.95
Placebo Group		
Week 0 (Baseline)	0.00 ± 0.00	3.48 ± 0.92
Week 6	0.85 ± 0.42	3.58 ± 0.85
Week 12	1.42 ± 0.65	3.72 ± 0.78

3.2.4 Multi-Target Synergistic Effects of Formula Active Ingredients on Clinical Outcomes

Clinical improvements in systemic inflammation, sebum production, skin barrier function, and post-inflammatory hyperpigmentation were attributed to the multi-target synergistic network of active ingredients. Each component contributed as follows:

High-absorption curcumin/THC: Inhibits the NF-κB pathway to downregulate IL-6 and block the

inflammatory cascade, representing the primary anti-acne and anti-inflammatory driver [12].

Fish oil: EPA and DHA competitively suppress arachidonic acid metabolism to reduce inflammatory mediators, enhancing anti-inflammatory efficacy in combination with curcumin [21].

Nicotinamide and zinc: Zinc inhibits 5α-reductase to reduce sebum synthesis; nicotinamide promotes ceramide production to strengthen the epidermal barrier [22].

Astaxanthin: Scavenges excess ROS to protect dermal collagen, and synergizes with nicotinamide to inhibit melanogenesis and reduce the melanin index [14].

Vitamin B6: Regulates hormonal balance and acts synergistically with zinc to control sebum secretion, reducing follicular hyperkeratosis and acne recurrence [23].

4. Discussion

This study systematically analyzed the clinical manifestations and pharmacokinetic characteristics of the novel high-absorption curcumin composition in the intervention of mild to moderate acne, providing high-quality evidence-based support for the efficient utilization of natural active ingredients with low bioavailability and nutritional intervention of inflammatory skin diseases. The experimental data clearly confirmed that the basic intestinal absorption rate of natural curcumin is only 0.33%, and more than 99.6% of the ingredients are rapidly metabolized and inactivated due to strong hydrophobicity, poor intestinal mucosal penetration and hepatic first-pass effect, failing to maintain an effective therapeutic concentration in vivo. This result is also highly consistent with the conclusion that the oral bioavailability of curcumin is less than 1% in previous studies [5,6]. After applying the dual delivery technology of supramolecular co-crystal and water-oil dual-phase fusion and adding exogenous active metabolite THC, the equivalent bioavailability of the composition was successfully increased to 98.02%. THC itself has far better chemical stability than the parent curcumin and can exert physiological activity directly without hepatic metabolic transformation [10]. High bioavailability effectively maintains the exposure of core active ingredients in the circulatory system, laying a foundation for the subsequent exertion of systemic anti-inflammatory and skin repair effects.

In the 12-week clinical intervention, the serum IL-6 concentration of subjects decreased by 48.09% compared with the baseline. As the core pro-inflammatory factor in the acne inflammatory cascade [24], the significant decrease in IL-6 level directly corresponded to a 52.41% reduction in inflammatory acne lesions, inhibiting the occurrence and development of acne from the root cause. In terms of ingredient synergy, nutritional factors such as fish oil, astaxanthin, nicotinamide, vitamin B6 and zinc in the composite formula formed a multi-pathway synergy with high-absorption curcumin/THC [13,14], ultimately reducing sebum secretion by 12.98% and increasing skin hydration by 17.53% in subjects, achieving the dual effects of oil control and skin barrier repair, improving the core inducements of acne pathogenesis from the pathophysiological level, and making up for the limitations of single curcumin intervention.

In addition, the ROS level in subjects decreased by 32.78% and the melanin index (MI) decreased by 11.37% after intervention. The significant improvement in antioxidant capacity not only reduces the continuous damage of oxidative stress to the skin [25], but also effectively improves post-inflammatory hyperpigmentation and relieves acne scars. The significant increase in subjects' subjective evaluation scores is also highly consistent with the improvement trend of various objective indicators, fully verifying that the composition not only improves the skin's physiological state, but also significantly enhances patients' quality of life and social confidence. In conclusion, the results show that the composition achieves multi-target effective intervention on mild to moderate acne by inhibiting inflammatory factors, balancing sebum secretion and repairing skin barrier function. It also confirms that advanced delivery platforms can effectively improve the

clinical efficacy of low-bioavailability natural products, providing a highly efficient and safe systemic intervention plan for inflammatory skin diseases, and an important experimental basis for the efficient utilization of natural active ingredients and the development of functional foods.

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