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TERPENOLOL: A NOVEL NANOMICELLAR, HYDROPHILIC CBD-DERIVED COMPOUND FOR PHARMACEUTICAL, NUTRACEUTICAL, COSMECEUTICAL, AND FUNCTIONAL FOOD APPLICATIONS

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ABSTRACT
Terpenolol is a newly developed hydrophilic derivative of cannabidiol (CBD) designed to overcome the solubility, stability, and pharmacokinetic limitations of conventional lipophilic CBD formulations. This study presents its physicochemical profile, 30-day stability, and preliminary pharmacokinetic behaviour in humans. Terpenolol forms a stable aqueous nanomicellar dispersion with neutral pH (7.0 ± 0.1), consistent viscosity, and minimal variation in tintometric and colloidal parameters over the observation period. In a single-dose, two-period crossover study involving five healthy volunteers, sublingual administration of Terpenolol resulted in markedly higher plasma CBD concentrations at 30 minutes compared with an oil-based reference formulation. Observational data from more than 200 individuals using Terpenolol-based preparations across oral, nasal, cutaneous, and transdermal routes indicate good tolerability and reported improvements in anxiety, panic symptoms, insomnia, psychotic- spectrum disturbances, and musculoskeletal or joint pain. The compound's complete solubility in aqueous media, combined with its neutral taste and odourless profile, also supports its incorporation into functional beverages, as demonstrated by a prototype mineral water formulation containing 50 mg of CBD in 500 ml. Overall, Terpenolol demonstrates physicochemical stability, improved early systemic exposure to CBD, and broad compatibility with formulations. Controlled studies are planned to further define its pharmacological relevance and potential application domains.

KEYWORDS: hydrophilic CBD derivative; nanomicellar CBD formulation; CBD pharmacokinetics; observational clinical data; CBD-based functional beverages.

1. INTRODUCTION

Cannabidiol (CBD) is a psychoactive but non-intoxicating phytocannabinoid derived from Cannabis sativa L. It exhibits antioxidant, anti-inflammatory, anxiolytic, neuroprotective, and anticonvulsant properties, with psychoactive effects mediated through serotonergic (5-HT1A), endocannabinoid, TRPV1, and adenosinergic pathways (Pisanti et al., 2017).

Despite its promising biological profile, CBD presents significant physicochemical limitations. It is highly lipophilic (logP ≈ 6–7), exhibits negligible aqueous solubility, and is prone to oxidative and thermal

degradation, compromising stability and shelf life in finished formulations (Alhadid et al., 2023;

Schwarzenberg et al., 2022). These constraints hinder its incorporation into hydrophilic systems and necessitate complex formulation strategies such as encapsulation, solubilisers, or stabilising excipients (Su & Zhang, 2024).

Several CBD-derivatives, including esters, glycosylated forms, and surfactant-like analogues have been explored to address these challenges. However, many of these compounds face limitations related to synthesis complexity, regulatory ambiguity, or restricted applicability across industrial sectors (Wang et al., 2023).

A persistent technological challenge remains: achieving true, instantaneous aqueous dissolution of a CBD-derived compound while maintaining neutral organoleptic properties, crystal clarity, and long-term physicochemical stability. Existing formulations often present compromises such as incomplete dispersion, undesirable sensory attributes, or limited shelf-life stability.

Terpenolol was specifically engineered to address this gap. It is a novel amphiphilic CBD- derived compound designed to combine the functional properties of CBD with enhanced solubility, stability, and formulation versatility. Its dual affinity for aqueous and lipid phases enables improved dispersibility in emulsions, gels, transdermal systems, and oral delivery matrices. Preliminary analyses indicate high chemical stability, minimal sensory impact, and broad compatibility with excipients commonly used in pharmaceutical, nutraceutical, and cosmeceutical formulations (Scrimali, 2020).

Derived from highly purified, THC-free industrial hemp biomass, Terpenolol aligns with current EU and US regulatory frameworks governing cannabinoid-based ingredients. Its formulation has been filed with the Italian Patent Office as a proprietary hydrophilic nanomicellar CBD composition, supporting its originality and industrial relevance. Its clean regulatory profile and scalable production process position it as a promising platform molecule for next-generation health and wellness products.

2. Characterisation of Terpenolol

2.1. Physicochemical Characterisation

Terpenolol forms a stable nanomicellar aqueous dispersion characterised by:

- pH: 7.0 ± 0.1
- Viscosity: Zahn Cup #1, 25 s at room temperature
- Appearance: slightly opalescent, homogeneous dispersion
- Mean nanomicellar diameter: ≈ 200 nanometers
- Organoleptic profile: neutral taste, no bitterness, no oily residue
- Tintometric analysis (Day 0): L* = 96.12, a* = –0.18, b* = +1.94

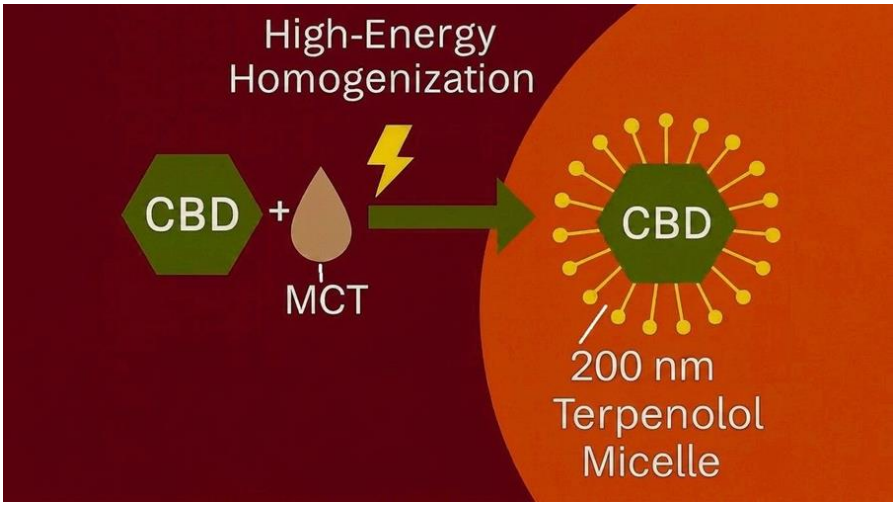

Figure 1: ***Schematic representation of Terpenolol formation from cannabidiol (CBD) and medium-chain triglycerides (MCT). The figure illustrates the amphiphilic architecture of Terpenolol, in which the CBD moiety is functionally integrated within a nanomicellar supramolecular structure. This micellar organisation confers hydrophilicity, improved aqueous dispersibility, and enhanced formulation versatility compared to conventional lipophilic CBD preparations.***

Following administration, Terpenolol disperses in aqueous biological fluids and gradually releases CBD in proximity to its molecular targets (e.g., 5-HT1A, TRPV1, endocannabinoid-related sites). This controlled release is hypothesised to support more efficient receptor engagement, reduced pharmacokinetic variability, and sustained functional effects compared to standard oil-based CBD formulations, while its interaction with CB1 is expected to occur via reversible biophysical modulation of membrane curvature and lipid-phase organisation, rather than via classical biochemical receptor activation.

Detailed schematic of Terpenolol's biophysical-allosteric mechanism: the ~200-nm nanomicellar structure perturbs the local lipid environment, inducing measurable variations in membrane curvature, lateral pressure profile, and surface tension. These physical changes are proposed to the transmembrane helices of CB1, producing a reversible shift in receptor conformation without orthosteric binding or canonical biochemical activation. The modulation is membrane-mediated, non-genomic, and rapidly dissipates upon nanomicellar washout, supporting fast, controllable, and mechanically driven influence on neuronal excitability.

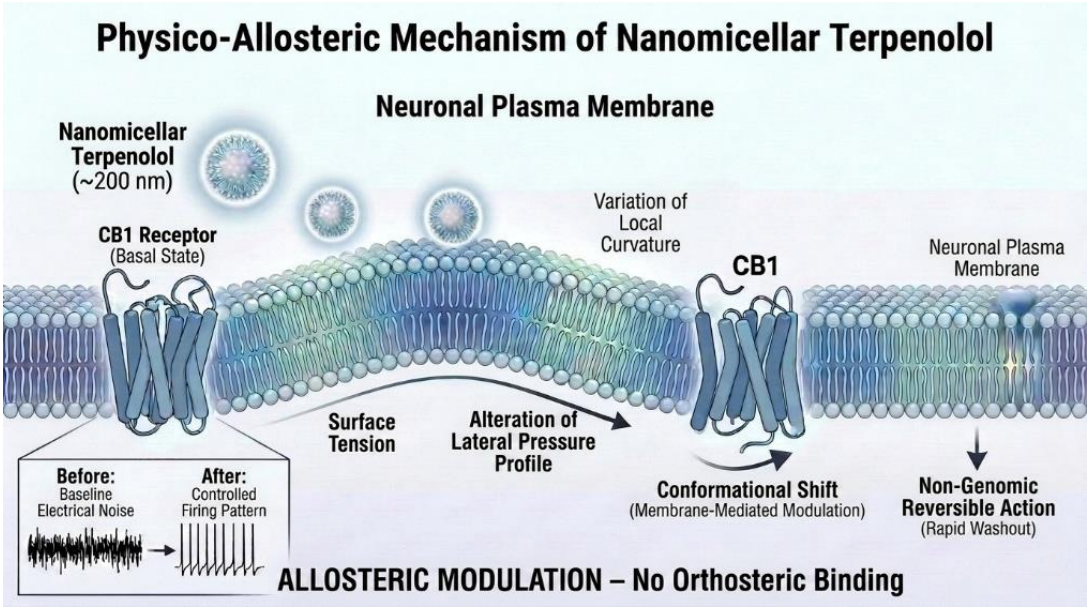

Figure 2: ***Detailed schematic of Terpenolol's biophysical-allosteric mechanism: the ~200-nm nanomicellar structure perturbs the local lipid environment, inducing measurable variations in membrane curvature, lateral pressure profile, and surface tension.***

2.2 Topographical Targeting of the Axonal and Perisynaptic Space

While conventional neuroactive agents primarily exert their biochemical mechanisms within the inter-synaptic cleft to alter neurotransmitter dynamics, Terpenolol shifts the anatomical focus of therapeutic intervention. Leveraging the native distribution of CB1 receptors—which neuroanatomical data demonstrates to be densely expressed along the pre-terminal axonal membrane and within perisynaptic regions—the nanomicellar formulation restricts its activity to the axonal compartment. This locus of action mirrors the operational principles of physical neuromodulation modalities. Analogous to transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), which target the axonal membrane to modulate polarization and electrical conductivity prior to synaptic transmission, Terpenolol modulates the exact same sub-cellular domain. Both approaches intervene along the axonal conduction pathway: electrophysiological instruments operate externally via bioelectric gradients, whereas Terpenolol acts internally as a fluid state biophysical modulator at the molecular level. By altering the biophysical properties of the axonal lipid bilayer before the action potential reaches the synaptic cleft, Terpenolol may contribute to stabilizing neuronal excitability at its source.

2.3 The Theory of Membrane Biophysical Modulation (MBM)

Given its immediate clinical onset and the absence of pharmacological tolerance, conventional biochemical models—predicated on slow, orthosteric "lock-and-key" binding to the CB1 receptor and subsequent intracellular second-messenger cascades—prove insufficient to explain this kinetic profile. Based on these observations, and preceding advanced experimental validation in three-dimensional rodent and human brain organoids, we propose the theory of Terpenolol as a Membrane Biophysical Modulator (MBM). The pharmacodynamics of Terpenolol are biophysical rather than biochemical. Upon interacting with the axonal plasma membrane, the ~200 nm nanomicelle instantaneously perturbs the local thermodynamic parameters of the lipid bilayer, modifying surface tension, altering local curvature, and remodelling the lateral pressure profile of the membrane. This mechanical deformation exerts a torsional force on the transmembrane helices of the CB1 receptor. This triggers a membrane-mediated allosteric conformational shift: the receptor's structural configuration and functional state are modulated by the physical state of the surrounding lipid microenvironment, bypassing the requirement for chemical occupancy of the orthosteric binding pocket. Upon nanomicelle washout, the lipid bilayer restores its baseline fluidity and the biophysical effect ceases, accounting for the complete reversibility of the mechanism.

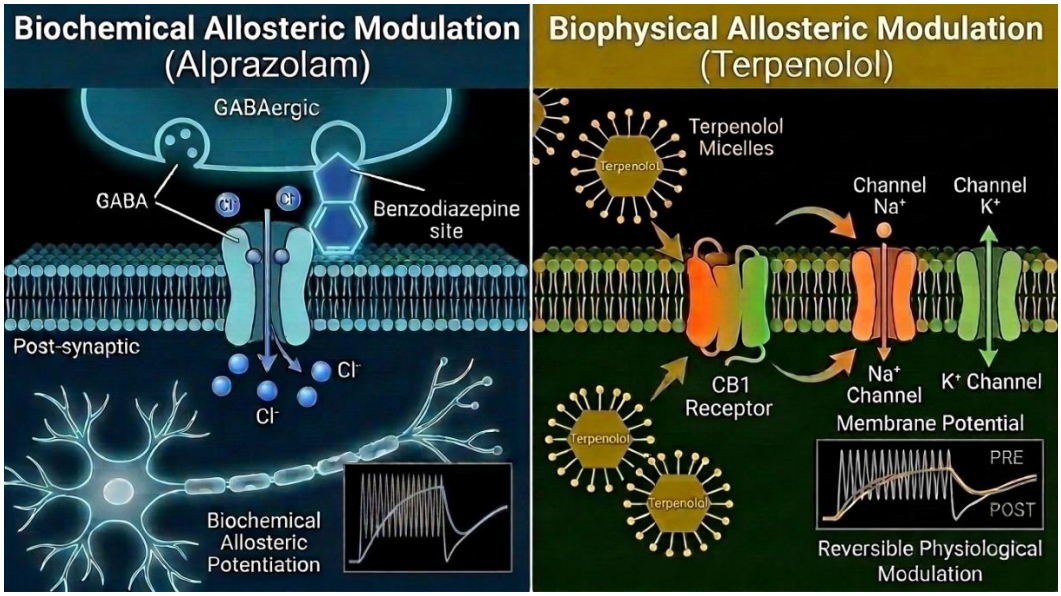

Figure 3*: The figure represents the two different mechanisms of action concerning Terpenolol and Alprazolam.*

Regulatory Classification: Substance-Based Medical Device Under EU MDR 2017/745

The biophysical mechanism of action established by Terpenolol is consistent with the current European regulatory paradigm for CE-marked Medical Devices. The European Medical Device Regulation (EU) 2017/745 (MDR) delineates a clear boundary: a product is qualified as a medical device provided its primary intended mode of action (MoA) is not achieved by pharmacological, immunological, or metabolic means. Because Terpenolol does not rely on classical orthosteric biochemical receptor binding, but rather operates via a purely mechanical, thermodynamic, and electrostatic perturbation of the cellular surface, the NegEnt product line incorporating Terpenolol has been classified and by the Italian Ministry of Health as a substance-based Medical Device. Consequently, Terpenolol does not function as an exogenous chemical entity that alters cellular metabolic pathways; instead, it acts as a biocompatible micro-architecture. It protects, stabilizes, and modulates tissue biological functions through a mechanical and physical modality, conceptually aligning with the intrinsic safety profile of electronic neuromodulation hardware (e.g., *PlatoWork).* This convergence between theoretical and regulatory considerations provides clinical investigators and practitioners with full medico-legal compliance grounded in an objective, state-of-the-art scientific framework.

2.4. Stability Study

A 30-day stability assessment was conducted at controlled room temperature (20-22 °C). Over the observation period:

pH remained constant at 7.0 ± 0.1

viscosity showed no significant variation

nanomicellar size distribution remained stable

tintometric parameters exhibited minimal fluctuations

tintometric analysis (Day 30): L* = 95.87, a* = –0.21, b* = +1.89.

The ΔE value remained below the perceptible threshold, confirming excellent chromatic stability and the absence of oxidative or structural degradation. These findings support the robustness of Terpenolol as a nanomicellar aqueous formulation suitable for long-term storage and diverse applications.

2.5. Pilot Pharmacokinetic Study

2.5.1. Study Design

A single-dose, open-label, two-period crossover pharmacokinetic study was conducted in five healthy adult volunteers (3 males, 2 females; age 28–54 years). The study compared:

• Terpenolol (hydrophilic CBD-derived compound)

• Standard oil-based CBD formulation (MCT-based reference)

Each participant received both formulations in randomized order, with a 7-day washout between periods. All participants provided informed consent.

2.5.2. Dosing and Administration

Each formulation delivered 25 mg of CBD:

• Terpenolol: 0.025 ml of the hydrophilic nanomicellar compound

• Oil-based CBD: 0.5 ml of a standard MCT-based CBD preparation

Both were administered sublingually, with subjects instructed to hold the liquid under the tongue for 60 seconds before swallowing.

2.5.3. Blood Sampling and Analysis

Venous blood samples were collected 30 minutes post-dose. Plasma CBD concentrations were quantified using HPLC-UV (220 nm). The method showed:

• Linearity: 1–500 ng/ml

• Intra-assay CV < 5%

• Inter-assay CV < 7%

• LLOQ: 1 ng/ml

2.5.4. Pharmacokinetic Results

Time (min)	Terpenolol (ng/ml ± SD)	Oil-based CBD (ng/ml ± SD)
30	32.6 ± 5.8	11.2 ± 3.4

At 30 minutes, Terpenolol achieved approximately 2.9-fold higher plasma CBD levels than the oil-based formulation, supporting a more efficient and predictable absorption profile.

3. Pharmacological Rationale and Intended Applications

The pharmacological profile of cannabidiol (CBD) supports its potential use across a wide range of neuropsychiatric and somatic conditions. Evidence from preclinical and clinical studies highlights CBD's anxiolytic, antipsychotic, anti-inflammatory, analgesic, and sleep-modulating properties, mediated through interactions with serotonergic (5-HT1A), endocannabinoid, TRPV1, and adenosinergic pathways (Coelho et al., 2024; Bhuller et al., 2024; Lavender et al., 2024; Fabris et al., 2024; Cásedas et al., 2024).

However, the clinical utility of conventional CBD formulations is limited by poor aqueous solubility, variable absorption, and inconsistent bioavailability. Terpenolol, as a hydrophilic CBD-derived compound with enhanced early systemic exposure, may stabilize or amplify CBD's functional effects. Its nanomicellar architecture facilitates rapid mucosal absorption, potentially reducing interindividual variability and enabling effective outcomes at lower doses.

These characteristics make Terpenolol particularly suitable for formulations intended for:

- rapid onset of action (e.g., sublingual or nasal delivery)
- prolonged or daily use
- applications requiring sensory neutrality
- integration into aqueous or semi-aqueous matrices
- multimodal therapeutic strategies, including those aligned with complex-systems-based approaches to mental health

Based on current evidence, Terpenolol may be relevant for:

- Anxiety disorders, including generalised anxiety and emotional dysregulation (Coelho et al., 2024)
- Panic disorder, particularly acute symptom management (Bhuller et al., 2024)
- Insomnia, especially when associated with hyperarousal or anxiety (Lavender et al., 2024)
- Psychotic-spectrum conditions, as an adjunctive or exploratory intervention (Fabris et al., 2024)
- Musculoskeletal and joint pain, including inflammatory components (Cásedas et al., 2024)
- Dermatological and mucosal inflammation, via topical or transdermal formulations

These potential applications are consistent with both CBD's known pharmacological actions and the enhanced bioavailability profile observed with Terpenolol.

4. Clinical Aspects (Scrimali, 2024)

Over a two-year period, Terpenolol was used in more than 200 patients through the NegEnt product line, which includes edible drops, nasal spray, cutaneous emulsions, and transdermal formulations. This real-world clinical experience was embedded within a broader therapeutic framework developed by Scrimali, who recently proposed a novel complex-systems-based approach to the treatment of mental disorders. This model, termed Complex Therapy, integrates cognitive-behavioural principles with systemic, neurobiological, and ecological dimensions of psychological functioning (Scrimali, 2024).

Treatment durations ranged from several weeks to multiple years. Data are on file and will be published soon. Across indications, patient-reported outcomes consistently highlighted improvements in emotional regulation, somatic tension, sleep quality, and pain.

4.1. Anxiety

Clinical experience indicates consistent reductions in generalized anxiety, improved emotional regulation, and decreased somatic tension. Sublingual and nasal formulations often produced rapid subjective relief.

4.2. Panic Attacks

In individuals with panic disorder, Terpenolol-based formulations—especially nasal spray and fast-acting drops—were associated with rapid attenuation of acute panic symptoms and improved autonomic control.

4.3. Insomnia

Patients with insomnia, particularly when comorbid with anxiety, reported improvements in sleep onset, reduced nocturnal awakenings, and enhanced subjective sleep quality.

4.4. Psychotic-Spectrum Disorders

Preliminary exploratory use in schizophrenia and schizoaffective disorders yielded encouraging observations, including reductions in agitation and improved emotional stability. These findings warrant structured clinical investigation.

4.5. Musculoskeletal and Joint Pain

Topical and transdermal Terpenolol formulations demonstrated analgesic and anti-inflammatory effects, with patients reporting reduced pain intensity, improved mobility, and decreased local discomfort.

4.6. Dermatological and Mucosal Inflammation

Early clinical experience in dermatitis, oral aphthae, and vulvovaginal irritation indicated favorable responses, including reduced inflammation and symptomatic relief.

Summary of Clinical Experience

Across all indications, Terpenolol was well tolerated, with no significant adverse events reported. Its hydrophilic nature, sensory neutrality, and compatibility

with multiple delivery routes facilitated prolonged use, including in sensitive populations such as children with anxiety, insomnia, or neurodevelopmental disturbances.

These real-world findings provide valuable preliminary insights into Terpenolol's potential therapeutic applications and support the rationale for future controlled clinical trials.

5. Tolerability and Safety (Scrimali, 2023)
Across all formulations and routes of administration, Terpenolol demonstrated a favorable safety and tolerability profile in real-world clinical use. More than 200 individuals were exposed to Terpenolol-based products over a two-year period, including sublingual drops, nasal spray, cutaneous emulsions, and transdermal preparations. No significant adverse events were reported.

Sublingual, nasal, cutaneous, and transdermal routes were consistently well tolerated. Patients did not report relevant irritation, excessive sedation, paradoxical reactions, or gastrointestinal discomfort. The hydrophilic nanomicellar architecture of Terpenolol, combined with its neutral taste and odorless profile, facilitated adherence and prolonged use.

Particularly noteworthy is the tolerability observed in sensitive populations, including children with anxiety, insomnia, or neurodevelopmental disturbances, who used Terpenolol-based formulations for extended periods without clinically relevant adverse effects. Although these observations are encouraging, they derive from uncontrolled real-world experience and should be interpreted cautiously.

The enhanced bioavailability associated with Terpenolol may allow effective outcomes at lower doses compared with conventional oil-based CBD formulations, potentially improving safety margins and reducing the risk of dose-related adverse effects.

Overall, the available evidence suggests that Terpenolol is a well-tolerated hydrophilic CBD-derived compound suitable for diverse delivery systems and prolonged use. Controlled studies are warranted to confirm these findings and to further characterize its safety profile.

6. Functional Foods, Wellness Beverages, and Hydra
The hydrophilic nature and nanomicellar organisation of Terpenolol, combined with its neutral taste and excellent organoleptic profile, make it particularly suitable for incorporation into functional foods, wellness beverages, and nutritional formulations. Unlike conventional CBD, which requires oily carriers and often alters taste, aroma, or clarity, Terpenolol dissolves instantly and uniformly in aqueous media, preserving transparency and sensory neutrality.

Terpenolol dissolves completely and uniformly in:
• water and mineral water
• tea and herbal infusions
• coffee and hot beverages
• fruit juices and smoothies
• wine, beer, and alcoholic beverages

This versatility enables the development of:
• wellness soft drinks
• mineral waters enriched with low-dose Terpenolol
• calming teas and functional coffees
• low-alcohol or alcohol-free beverages with added wellness attributes

Hydra – Proof of Concept
A prototype wellness beverage, provisionally named ***Hydra***, was developed using:
• 0.5 L of still or sparkling mineral water
• 50 mg of CBD, corresponding to 0.05 ml of Terpenolol

Terpenolol dissolved instantly and completely, without altering taste, clarity, or effervescence. Informal sensory evaluation indicated that Hydra was refreshing, pleasant, and suitable for daily consumption. These findings suggest promising applications in wellness, hydration, and emotional and physical well-being.

7. DISCUSSION
This study provides the first comprehensive characterisation of Terpenolol, a novel hydrophilic CBD-derived compound designed to overcome the intrinsic limitations of conventional lipophilic cannabidiol preparations. Physicochemical analyses demonstrated that Terpenolol forms a stable nanomicellar dispersion with neutral pH (7.0 ± 0.1), consistent viscosity, stable tintometric parameters, and a reproducible organoleptic profile over at least 30 days. These features indicate that the compound possesses a robust formulation profile suitable for diverse pharmaceutical, nutraceutical, cosmeceutical, and food-grade applications.

The pharmacokinetic findings further support the translational relevance of Terpenolol. In a controlled crossover study, the compound achieved markedly higher plasma CBD concentrations 30 minutes after sublingual administration compared to a standard oil-based formulation, with a faster time to peak and reduced interindividual variability. This enhanced systemic exposure is consistent with the hydrophilic nanomicellar architecture of Terpenolol, which likely facilitates more efficient mucosal absorption and reduces the variability typically associated with lipophilic CBD products. Improved bioavailability may allow for lower effective doses, potentially enhancing safety and tolerability.

Beyond laboratory and pharmacokinetic data, Terpenolol has undergone extensive real-world clinical use through the NegEnt product line. Over a two-year period, more than 200 patients were treated for anxiety, panic attacks, insomnia, musculoskeletal pain, dermatological

inflammation, and mucosal irritation. Clinical observations indicate consistent improvements in anxiety symptoms, rapid attenuation of acute panic episodes, enhanced sleep quality, and meaningful reductions in musculoskeletal discomfort. Preliminary results in psychotic-spectrum disorders and inflammatory dermatological conditions are encouraging and warrant further investigation.

A distinctive element emerging from this experience is the exceptional manageability of Terpenolol across its various formulations. The compound's hydrophilic nature, pleasant organoleptic profile, and absence of significant adverse effects have facilitated prolonged use, including in sensitive populations such as children with anxiety, insomnia, or neurodevelopmental disturbances. The favorable tolerability profile observed in both the pharmacokinetic study and clinical practice aligns with the known safety characteristics of CBD, while the improved bioavailability of Terpenolol may allow for effective outcomes at reduced dosages.

An additional and promising domain is the food and wellness beverage industry, where Terpenolol's complete solubility in aqueous media represents a major technological advantage. Unlike conventional CBD, which requires oily carriers and often alters taste or appearance, Terpenolol dissolves instantly and uniformly in water, mineral water, tea, coffee, juices, wine, beer, and alcoholic beverages. The development of Hydra, a mineral water enriched with 50 mg of CBD derived from 0.05 ml of Terpenolol, provides a compelling proof of concept. The beverage preserved clarity, taste, and effervescence, and was perceived as refreshing and suitable for daily wellness hydration.

Taken together, these findings position Terpenolol as a next-generation hydrophilic CBD-derived compound with broad translational potential. Its physicochemical stability, enhanced pharmacokinetic performance, excellent tolerability, and versatility across pharmaceutical, nutraceutical, cosmeceutical, and food-grade formulations suggest that Terpenolol may represent a potentially meaningful advancement in cannabinoid science. While the real-world clinical observations reported here provide valuable preliminary insights, controlled clinical trials and further formulation studies will be essential to fully validate the therapeutic and industrial potential of Terpenolol and to delineate its role within the evolving landscape of cannabinoid-based compounds.

It is important to acknowledge the preliminary nature and inherent limitations of the current research on Terpenolol, particularly concerning the scale of pharmacokinetic and observational studies. As a small non-profit organisation dedicated to phytopharmaceutical research (ALETEIA Lab for Phytopharmaceutical Research), these initial findings serve as a crucial foundational step. We are committed to a comprehensive and robust research programme, with extensive studies on Terpenolol's pharmacokinetics, pharmacodynamics, toxicology, and controlled clinical efficacy.

8. CONCLUSIONS

Terpenolol emerges from this study as a novel hydrophilic CBD-derived compound with a unique combination of physicochemical stability, enhanced pharmacokinetic performance, excellent tolerability, and remarkable versatility across multiple formulation environments. Its nanomicellar architecture enables complete solubility in aqueous media, overcoming the intrinsic limitations of conventional lipophilic CBD preparations and opening new possibilities for pharmaceutical, nutraceutical, cosmeceutical, and food-grade applications.

The compound demonstrated robust stability over time, maintaining consistent pH, viscosity, tintometric parameters, and nanomicellar structure. Pharmacokinetic evaluation revealed significantly improved systemic exposure following sublingual administration, supporting the hypothesis that Terpenolol's hydrophilic nature facilitates more efficient mucosal absorption.

These findings align with the extensive real-world clinical experience accumulated through the NegEnt product line, where more than 200 patients were treated across a range of conditions with excellent tolerability and meaningful clinical improvements.

A particularly innovative aspect of Terpenolol is its suitability for functional foods and wellness beverages, as demonstrated by the successful development of Hydra, a mineral water enriched with 50 mg of CBD. The compound dissolved instantly and completely, preserving taste and clarity, and illustrating its potential as a next-generation ingredient for wellness hydration and nutritional applications.

These findings should be interpreted as an initial conceptualisation of a novel hydrophilic CBD-derived platform rather than as definitive mechanistic or clinical proof. While Terpenolol offers a promising strategy to address CBD's solubility and early systemic exposure limitations, several of the mechanistic and therapeutic hypotheses advanced herein remain preliminary and partially speculative.

Definitive validation will require a staged research program including: comprehensive chemical characterisation and impurity profiling; rigorous biophysical investigations on model membranes and receptor microenvironments to substantiate membrane-mediated allosteric effects; expanded pharmacokinetic studies with dense sampling and LC-MS/MS quantification to define Cmax, Tmax, AUC and interindividual variability; GLP-compliant toxicology and safety studies; and adequately powered, controlled clinical trials.

A validation program to pursue these objectives is currently underway under the direction of the author, Tullio Scrimali. Securing independent replication and appropriate funding is essential to translate the present conceptual innovation into a reproducible scientific paradigm and into safe, evidence-based therapeutic and industrial applications.

Author Contributions: Tullio Scrimali: study design, scientific supervision, data interpretation, manuscript drafting. Advanced artificial intelligence tools: statistical data processing, support in text structuring, translation into English, linguistic optimisation, and formal revision. Scientific responsibility for all content remains entirely with the human author.

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