

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tetrahydropalmatine

A plant-derived protoberberine alkaloid from Corydalis yanhusuo and Stephania rotunda with documented dopamine D1/D2/D3 receptor antagonism, analgesic and sedative properties rooted in centuries of traditional Chinese medicine use, and an emerging clinical research profile in substance use disorders, neuropathic pain, and neuropsychiatric applications.

DOCUMENT	KDC-MN-1616
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Tetrahydroprotoberberine isoquinoline alkaloid with multi-target dopamine receptor antagonism and analgesic, sedative, and anti-addictive activity

ABSTRACT

Tetrahydropalmatine (THP), also known as rotundine, is a tetrahydroprotoberberine isoquinoline alkaloid isolated from tubers of *Corydalis yanhusuo* (Yan Hu Suo) and roots of *Stephania rotunda*, two genera of the Papaveraceae and Menispermaceae families with extensive histories in traditional Chinese and Southeast Asian medicine. The compound exists as two enantiomers: levo-tetrahydropalmatine (l-THP, the 13aR configuration) and dextro-tetrahydropalmatine (d-THP, the 13aS configuration), as well as the racemic mixture (dl-THP). The levorotatory enantiomer is the principal pharmacologically active form and has been manufactured as a pharmaceutical product in China under the name rotundine for the treatment of pain and insomnia since the mid-twentieth century. Molecular pharmacology studies have established that l-THP acts as a moderate-affinity antagonist at dopamine D1 receptors (K_i approximately 124 nM), dopamine D2 receptors (K_i approximately 388 nM), and dopamine D3 receptors, with additional binding at serotonin 5-HT1A receptors (K_i approximately 340 nM), α -1 adrenergic receptors, and modulatory effects on GABAergic neurotransmission through enhancement of GABA-A receptor activity. This multi-target monoaminergic profile distinguishes tetrahydropalmatine from conventional dopamine antagonists and underwrites the compound's diverse pharmacological actions: analgesia in inflammatory and neuropathic pain models, sedation and anxiolysis, attenuation of drug-seeking behavior in cocaine, heroin, and nicotine self-administration paradigms, and anti-inflammatory activity through suppression of NF-kappaB signaling and proinflammatory cytokine release.

Pharmacokinetics in humans are characterized by rapid absorption (absorption half-life approximately 0.5 hours), rapid distribution (distribution half-life approximately 0.74 hours), and slow

elimination (elimination half-life approximately 11.4 hours). Oral bioavailability is low due to extensive first-pass hepatic metabolism, principally through CYP3A and CYP1A2 isoforms, with stereoselective differences between enantiomers. Self-microemulsifying drug delivery systems have demonstrated a 3.25-fold improvement in relative bioavailability compared with conventional suspension formulations. The compound crosses the blood-brain barrier and achieves central nervous system concentrations sufficient for dopaminergic and serotonergic receptor modulation at therapeutic oral doses.

Clinical evidence is modest but growing. A randomized, double-blind, placebo-controlled Phase 1 study in cocaine users (2016) established the safety and tolerability of a 3.5-day oral l-THP course. A pilot clinical study in heroin-dependent patients demonstrated that one-month l-THP treatment significantly reduced opiate craving and enhanced the abstinence rate three-fold at three months post-discharge. A randomized controlled trial of l-THP as adjunctive treatment for schizophrenia (NCT02118610, published 2020) did not demonstrate significant improvement in psychiatric symptoms at 30 mg twice daily for four weeks, though the study confirmed tolerability and absence of serious adverse events. The compound has been marketed as a sedative-analgesic in China for decades and is under active investigation in the United States and Vietnam for substance use disorders.

The principal safety signals are sedation (dose-dependent, reflecting the composite dopaminergic and GABAergic mechanism), hepatotoxicity (reported in association with herbal preparations containing l-THP, though causality is confounded by product adulteration and polypharmacy), and rare acute poisoning characterized by mild neurological disturbance with rapid recovery. This monograph documents the chemistry, stereochemistry, and natural sources of tetrahydropalmatine; the multi-receptor pharmacology in molecular and behavioral detail; the pharmacokinetic record including CYP isoform involvement

and bioavailability optimization; the preclinical pharmacology across pain, addiction, neuroinflammation, and neuroprotection models; the clinical evidence base; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety signal; and a comparative assessment of five alternative analgesic or dopaminergic compounds against tetrahydropalmatine on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Not assigned (tetrahydropalmatine is not an INN-designated compound; it is identified by its chemical name in pharmacopoeial and regulatory contexts).

Common names and synonyms: Tetrahydropalmatine (THP), rotundine (the levorotatory enantiomer, used as a pharmaceutical name in China and Vietnam), Yan Hu Suo Yi Su (Chinese pharmaceutical nomenclature), corydalis B, gindarine.

Marketed names: Rotundine tablets (China, various manufacturers); Rotunda (Vietnam); Jin Bu Huan Anodyne Tablets (United States, herbal product, subsequently withdrawn from market due to hepatotoxicity reports associated with the formulation).

Chemical Abstracts Service registry numbers: 2934-97-6 (racemic dl-tetrahydropalmatine), 483-14-7 (levo-tetrahydropalmatine, the 13aR enantiomer), 3520-14-7 (dextro-tetrahydropalmatine, the 13aS enantiomer), 6024-85-7 (tetrahydropalmatine hydrochloride salt).

International Union of Pure and Applied Chemistry name: (13aR)-5,8,13,13a-tetrahydro-2,3,9,10-tetramethoxy-6H-dibenzo[a,g]quinolizine (for the levorotatory enantiomer). The racemic form is designated without the stereochemical prefix.

Clinical trial identifiers: NCT02118610 (l-THP as adjunctive treatment for schizophrenia, University of Maryland); additional Chinese clinical trial registrations for analgesic and addiction indications.

1.2 Structural class and chemistry

Tetrahydropalmatine belongs to the tetrahydroprotoberberine subclass of isoquinoline alkaloids, a structurally diverse family of plant-derived nitrogen-containing heterocyclic compounds that includes berberine, palmatine, coptisine, and related protoberberines. The tetrahydroprotoberberine scaffold consists of a dibenzo[a,g]quinolizine ring system with four fused rings (designated A, B, C, and D), where rings A and D are aromatic and rings B and C are partially saturated. Tetrahydropalmatine is distinguished from other members of this subclass by the presence of four methoxy substituents at positions 2, 3, 9, and 10 on the aromatic rings [1, 2].

Molecular formula: C₂₁H₂₅NO₄.

Exact mass: 355.1784 g/mol (monoisotopic).

Molecular weight: 355.43 g/mol (free base); 391.89 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline powder. Sparingly soluble in water as the free base; freely soluble in water as the hydrochloride salt. Soluble in methanol, ethanol, chloroform, and dimethyl sulfoxide. Melting point of the free base is approximately 143 to 145 degrees Celsius. The hydrochloride salt melts at approximately 265 to 268 degrees Celsius with decomposition.

Stereochemistry: Tetrahydropalmatine contains one chiral center at carbon 13a of the quinolizine ring system. The levorotatory enantiomer (l-THP) has the 13aR absolute configuration and is the pharmacologically preferred form with greater potency at dopamine receptors and more pronounced analgesic and sedative activity. The dextrorotatory enantiomer (d-THP, 13aS configuration) exhibits distinct receptor binding preferences, with relatively greater affinity for D1 receptors. The racemic mixture (dl-THP) has been used in many pharmacological studies and in some commercial preparations. Investigators acquiring research-grade material should confirm enantiomeric identity and purity by chiral high-performance liquid chromatography or polarimetry.

1.3 Natural sources

Tetrahydropalmatine is a major constituent alkaloid of several plant species in the Papaveraceae and Menispermaceae families. The principal botanical sources are:

Corydalis yanhusuo (Yan Hu Suo): The tubers of this species, native to eastern China and cultivated extensively in the Zhejiang and Jiangsu provinces since the Ming Dynasty, are the traditional and commercial source of tetrahydropalmatine. The alkaloid content in dried tubers ranges from approximately 0.08 to 0.15 percent by weight, with tetrahydropalmatine representing one of approximately 20 protoberberine alkaloids identified in the plant [3, 4].

Stephania rotunda: The roots of this Southeast Asian species, particularly abundant in Vietnam, Cambodia, and Thailand, contain l-THP at yields of approximately 1.2 to 1.5 percent. The Vietnamese scientist Sang Dinh Bui first isolated the compound from this source in 1940 and named it rotundin (subsequently rotundine) [5].

Other Corydalis species: *C. ambigua*, *C. decumbens*, *C. cava*, and *C. solida* contain varying quantities of tetrahydropalmatine and related protoberberine alkaloids.

1.4 Synthesis

Tetrahydropalmatine can be obtained through extraction from plant material or through chemical synthesis. The biosynthetic pathway in plants proceeds from tyrosine through (S)-reticuline to the protoberberine scaffold via the berberine bridge enzyme, followed by methylation and reduction steps [6].

Chemical synthesis of tetrahydropalmatine has been accomplished through several routes. The most direct approach involves the reduction of palmatine (the fully aromatic protoberberine quaternary alkaloid), in which the C-C double bond and C-N double bond of the berberine ring system are reduced by catalytic hydrogenation or by sodium borohydride to yield the racemic tetrahydro product [7]. Resolution of the racemate to obtain the 1-THP enantiomer is accomplished by chiral HPLC or by diastereomeric salt crystallization with chiral acids such as dibenzoyl-L-tartaric acid.

Total synthesis approaches have also been reported, typically involving Pictet-Spengler cyclization of appropriately substituted phenylethylamine and aldehyde precursors to construct the isoquinoline ring system, followed by Bischler-Napieralski cyclization or related strategies to close the fourth ring. These multi-step syntheses are generally less efficient than extraction or semisynthesis from palmatine for bulk production. Industrial manufacturing in China relies predominantly on extraction from cultivated *Corydalis yanhusuo* tubers with subsequent purification by column chromatography and recrystallization.

2. Abstract

Tetrahydropalmatine (THP) is a tetrahydroprotoberberine isoquinoline alkaloid with multi-target pharmacology centered on moderate-affinity dopamine receptor antagonism, analgesic activity in inflammatory and neuropathic pain models, sedative and anxiolytic effects, and attenuation of drug-seeking and drug-reinforced behavior across multiple substances of abuse. The compound has been used as a pharmaceutical analgesic and sedative in China for over half a century and is the subject of active clinical investigation in the United States for substance use disorders and neuropsychiatric applications [8, 9].

The pharmacological profile of l-THP is distinguished by antagonism at dopamine D1 (K_i approximately 124 nM), D2 (K_i approximately 388 nM), and D3 receptors; binding at serotonin 5-HT_{1A} receptors (K_i approximately 340 nM); antagonism at α -1 adrenergic receptors; and enhancement of GABAergic neurotransmission through GABA-A receptor modulation [10, 11, 12]. This composite monoaminergic and GABAergic profile produces a pharmacological signature that does not map onto any single conventional drug class. The dopamine receptor antagonism at D1 and D2 subtypes is sufficient to modulate mesolimbic reward circuitry without the potency to produce extrapyramidal symptoms at analgesic or sedative doses, a distinction that has motivated the investigation of l-THP as a non-addictive alternative to opioid analgesics and benzodiazepine anxiolytics.

Preclinical evidence is substantial across multiple therapeutic domains. In pain models, l-THP produces dose-dependent analgesia in inflammatory pain (complete Freund's adjuvant, bee venom, formalin), neuropathic pain (spared nerve injury, chronic constriction injury), and visceral pain paradigms, with mechanisms involving suppression of spinal TRPV1 and P2X₃ receptor expression, inhibition of p38 MAPK/NF- κ B/iNOS signaling, and glial cell deactivation [13, 14, 15]. In addiction models, l-THP attenuates cocaine, heroin, and nicotine self-administration and reinstatement of extinguished drug-seeking behavior in rats, with the mechanism attributed to blockade of dopaminergic reward signaling in the nucleus accumbens [16, 17, 18]. In neuroinflammation and neuroprotection models, THP reduces proinflammatory cytokine release (TNF- α , IL-1 β , IL-6) through NF- κ B pathway suppression, protects against ischemia-reperfusion injury, and attenuates heatstroke-induced neurological damage [19, 20].

Clinical evidence is more limited. The compound has been marketed in China for decades for the treatment of pain and insomnia, establishing a population-level safety record. A United States Phase 1 study in cocaine users (Marcenac et al. 2016) demonstrated safety and tolerability of short-course oral l-THP [21]. A pilot study in heroin-dependent patients demonstrated significant reduction in opiate craving and three-fold increase in abstinence rate at three-month follow-up [22]. A randomized controlled trial of l-THP as adjunctive treat-

ment for schizophrenia (Bhatt et al. 2020) did not demonstrate efficacy on psychiatric endpoints at 30 mg twice daily [23]. The current clinical-research state is therefore one of established safety, modest efficacy data in addiction populations, negative results in the schizophrenia adjunctive indication, and ongoing investigation in substance use disorders and pain.

3. Discovery and Development History

3.1 Traditional medicine origins

The medicinal use of *Corydalis yanhusuo* (Yan Hu Suo) in Chinese traditional medicine is documented from at least the Tang Dynasty. The earliest known reference appears in the *Ben Cao Shi Yi* (Omissions from the Materia Medica), written by Chen Cang-Qi in approximately 720 CE. The herb was classified as an analgesic (*huo xue, zhi tong*) and was recommended for chest pain, abdominal pain, dysmenorrhea, and traumatic injury pain. The famous aphorism from the *Lei Gong Pao Zhi Lun*, "When heart pain threatens death, seek Yan Hu Suo with haste," reflects the prominent position of *Corydalis* tubers in the classical Chinese pain pharmacopoeia [3].

During the Tang and Song Dynasties, the herb was collected from wild populations of northeastern *Corydalis* species. From the Ming Dynasty onward, cultivation of *C. yanhusuo* in the Zhejiang and Jiangsu provinces became standard practice, and the cultivated southern variety gradually replaced wild northern material as the principal commercial source [4].

3.2 Isolation and identification of the active alkaloid

The isolation of tetrahydropalmatine from *Corydalis* species was accomplished by multiple research groups in the early to mid-twentieth century as part of the broader effort to characterize the alkaloid constituents of traditional Chinese medicinal plants. In 1940, the Vietnamese scientist Sang Dinh Bui independently isolated the levorotatory enantiomer from the roots of *Stephania rotunda* and named the compound *rotundin*, establishing the parallel Southeast Asian pharmacological tradition [5].

The structural elucidation of tetrahydropalmatine as a tetramethoxy-substituted tetrahydroprotoberberine was accomplished through degradation chemistry and spectroscopic methods in the 1950s and 1960s, confirming the compound's membership in the isoquinoline alkaloid family and its relationship to palmatine (the fully oxidized protoberberine).

3.3 Pharmaceutical development in China

Following isolation and structural characterization, l-THP (*rotundine*) was developed as a pharmaceutical product in China during the 1950s and 1960s. The compound was introduced into clinical practice as a sedative-analgesic alternative to opioid analgesics and barbiturate sedatives, with the advantages of non-addictiveness and a wider therapeutic index.

Rotundine tablets (typically 30 to 60 mg per dose) were manufactured by multiple Chinese pharmaceutical companies and were included in the Chinese Pharmacopoeia as a recognized medicinal substance [8].

The pharmaceutical positioning of l-THP in China exploited the compound's unique pharmacological profile: analgesic activity without opioid receptor agonism, sedation without the physical dependence liability of benzodiazepines, and anxiolysis without the respiratory depression risk of barbiturates. This positioning has been maintained through decades of clinical use, and the compound remains available as a prescription and over-the-counter medicine in China and Vietnam.

3.4 Western research interest and clinical development

Interest in tetrahydropalmatine in Western pharmacology accelerated in the 2000s with the characterization of its dopamine receptor antagonist profile and the recognition of its potential in substance use disorders. The observation that l-THP attenuated cocaine self-administration in rats (Mantsch et al. 2007) established the preclinical foundation for the addiction research program [16]. Subsequent demonstrations of efficacy in heroin and nicotine self-administration models expanded the scope of interest [17, 18].

The United States Food and Drug Administration granted Investigational New Drug status for l-THP, and the first United States clinical trial (NCT02118610) was conducted at the University of Maryland School of Medicine as a randomized, double-blind, placebo-controlled study of l-THP as adjunctive treatment for schizophrenia. This trial, which enrolled 63 adults, was published by Bhatt et al. in *Schizophrenia Bulletin Open* in 2020 [23]. Parallel clinical investigation of l-THP for cocaine use disorder has been conducted with support from the National Institute on Drug Abuse.

In Vietnam, clinical trials conducted with international support have validated the effectiveness and safety of l-THP as a detoxification treatment for opioid withdrawal, building on the traditional use of *Stephania rotunda* in Vietnamese folk medicine [24].

4. Mechanism of Action

Tetrahydropalmatine is a multi-target ligand whose principal molecular activities are dopamine receptor antagonism across D1, D2, and D3 subtypes; serotonin receptor binding at the 5-HT_{1A} subtype; α -1 adrenergic receptor antagonism; and modulation of GABAergic neurotransmission. These activities operate at functionally relevant concentrations and contribute differentially to the observed analgesic, sedative, anxiolytic, anti-addictive, and anti-inflammatory effects.

4.1 Dopamine receptor antagonism

The dopamine receptor system comprises five subtypes (D1 through D5), classified into D1-like (D1, D5) and D2-like (D2, D3, D4) families. Tetrahydropalmatine, particularly the l-enantiomer, acts as a competitive antagonist at D1 and D2 receptors with moderate affinity. Reported K_i values for l-THP are approximately 124 nM at D1 receptors and approximately 388 nM at D2 receptors, with additional binding at D3 receptors at similar or slightly lower affinity [10, 11].

The D1 receptor antagonism contributes to the attenuation of stimulus-reward associations that drive drug-seeking behavior. The D2 receptor antagonism modulates mesolimbic dopaminergic transmission in the ventral tegmental area and nucleus accumbens, the canonical reward circuitry implicated in the reinforcing properties of cocaine, heroin, nicotine, and other substances of abuse. The moderate affinity of l-THP at D2 receptors (approximately 100-fold lower than haloperidol) is sufficient to modulate reward signaling without producing the acute extrapyramidal symptoms, prolactin elevation, or catalepsy characteristic of high-potency D2 antagonists at antipsychotic doses [25].

The d-enantiomer (d-THP) demonstrates a pharmacological profile that partially overlaps with l-THP but with preferential D1 receptor affinity and distinct downstream behavioral consequences. The enantiomeric selectivity is a pharmacologically meaningful distinction and is the basis for the preference for l-THP in clinical and research applications targeting addiction and pain [10].

4.2 Serotonin receptor binding

L-THP binds at serotonin 5-HT_{1A} receptors with a K_i of approximately 340 nM. The 5-HT_{1A} receptor is a Gi/Go-coupled inhibitory receptor expressed at high density on serotonergic neurons of the dorsal raphe (as an autoreceptor) and on postsynaptic neurons in the hippocampus, cortex, and limbic system. Activation or partial agonism at 5-HT_{1A} receptors is associated with anxiolytic and antidepressant effects; the functional consequence of l-THP

binding at this receptor (whether agonist, partial agonist, or antagonist) has not been fully characterized in published literature, though the anxiolytic behavioral profile of l-THP in the elevated plus-maze and other anxiety paradigms is consistent with a 5-HT1A-mediated contribution [12, 26].

4.3 Alpha-1 adrenergic receptor antagonism

L-THP demonstrates antagonism at alpha-1 adrenergic receptors, contributing to its sedative and hypotensive properties. The alpha-1 adrenergic receptor is expressed on vascular smooth muscle, in the central nervous system (locus coeruleus, cortex), and on peripheral sympathetic nerve terminals. Blockade of central alpha-1 receptors reduces noradrenergic arousal tone and contributes to the sedative profile. The magnitude of alpha-1 antagonism relative to dopaminergic blockade varies with dose and contributes to the dose-dependent sedation observed at higher oral doses [11].

4.4 GABAergic modulation

Research indicates that l-THP modulates GABAergic neurotransmission through enhancement of GABA-A receptor activity, though the precise molecular mechanism (direct allosteric modulation, indirect facilitation through monoaminergic effects, or both) has not been fully delineated. Enhancement of GABAergic inhibitory tone contributes to the sedative, anxiolytic, and muscle relaxant properties and provides a mechanistic basis for the compound's efficacy in insomnia, distinct from the dopaminergic contribution to sleep induction through suppression of dopaminergic arousal circuits [27].

4.5 Anti-inflammatory signaling

THP suppresses NF-kappaB-driven proinflammatory cytokine release, including TNF-alpha, IL-1beta, and IL-6, through inhibition of the TLR4/NF-kappaB/NLRP3 signaling pathway. In acute lung injury models, THP induced polarization of M1 macrophages to the M2 phenotype, reducing tissue inflammation and restoring PI3K/AKT/mTOR-mediated autophagy [19, 20]. The anti-inflammatory mechanism operates independently of the dopaminergic pharmacology and provides a separate therapeutic axis for conditions involving neuroinflammation, peripheral inflammation, and ischemia-reperfusion injury.

4.6 Analgesic signaling pathways

The analgesic mechanism of THP involves multiple spinal and supraspinal pathways. At the spinal level, THP suppresses expression of transient receptor potential vanilloid 1 (TRPV1) and purinergic P2X3 receptors on dorsal horn nociceptive neurons, reducing peripheral nociceptive transmission [14]. THP also inhibits the p38 MAPK/NF-kappaB/iNOS signaling cascade in the spinal cord, reducing nitric oxide production and neuroinflammation in neuro-

pathic pain states [13]. Additionally, THP promotes apoptosis and inhibits activation of spinal glial cells (astrocytes and microglia), which are recognized contributors to central sensitization and the maintenance of chronic pain [15]. At the supraspinal level, dopaminergic modulation of descending pain-inhibitory pathways and serotonergic modulation through 5-HT1A receptors contribute to the composite analgesic effect.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

L-tetrahydropalmatine is absorbed from the gastrointestinal tract after oral administration, but bioavailability is low due to poor aqueous solubility of the free base, extensive first-pass hepatic metabolism, and P-glycoprotein-mediated efflux. The absorption half-life in human volunteers is approximately 0.5 hours, indicating rapid uptake from the intestinal lumen [28]. However, the absolute oral bioavailability of conventional tablet formulations has been estimated at approximately 20 to 30 percent in animal models, limiting the efficiency of oral dosing.

Self-microemulsifying drug delivery systems (SMEDDS) have been developed to overcome the bioavailability limitation. In pharmacokinetic comparison studies, SMEDDS formulations produced a 3.25-fold increase in the relative bioavailability of l-THP compared with conventional suspension formulations, with correspondingly higher peak plasma concentrations and longer duration of therapeutic plasma levels [29].

5.2 Distribution

L-THP has a moderate to large volume of distribution, consistent with extensive tissue partitioning. The compound crosses the blood-brain barrier effectively, as demonstrated by both pharmacological effects (central sedation and analgesia at oral doses) and by direct brain tissue concentration measurements in rat pharmacokinetic studies. Brain-to-plasma ratios in rats exceed unity, indicating preferential central nervous system accumulation. The distribution half-life in humans is approximately 0.74 hours [28].

Plasma protein binding has been characterized but comprehensive data across species are limited. The compound distributes into liver, kidney, brain, and lung tissue, with the liver representing the principal site of metabolic clearance.

5.3 Metabolism

Tetrahydropalmatine is metabolized predominantly in the liver by cytochrome P450 enzymes. The principal metabolic pathways are O-demethylation, hydroxylation, and N-dealkylation, producing multiple oxidized metabolites that are subsequently conjugated (glucuronidation and sulfation) and excreted in urine and bile [30].

The CYP isoforms involved in THP metabolism demonstrate stereoselective preferences. In rat liver microsomes, CYP3A1/2 preferentially metabolizes the d-enantiomer, whereas CYP1A2 preferentially metabolizes the l-enantiomer. In human systems, CYP3A4, CYP1A2, and CYP2D6 are all involved in the oxidative metabolism of THP [30, 31].

Importantly, THP itself modulates CYP enzyme activity, creating the potential for pharmacokinetic drug-drug interactions. D-THP inhibits CYP2D6 and CYP1A2 isozyme activities, whereas l-THP inhibits CYP1A2 activity and induces CYP3A4 and CYP2C9 activities. In beagle dog studies, THP increased the AUC of midazolam (a CYP3A probe substrate) by 39 to 57 percent and decreased the 1-hydroxymidazolam/midazolam metabolite ratio by 22 to 29 percent, consistent with clinically meaningful CYP3A4 inhibition [32].

5.4 Elimination

The elimination half-life of l-THP in humans is approximately 11.4 hours, supporting once-daily or twice-daily dosing schedules [28]. Elimination is predominantly metabolic, with renal excretion of conjugated metabolites as the primary route. Less than 5 percent of an administered dose is excreted unchanged in urine.

In spontaneously hypertensive rats, the pharmacokinetics of THP differ from those in normotensive rats, with altered clearance and distribution parameters, suggesting that cardiovascular disease states may affect THP disposition [33].

5.5 Routes of administration

The primary route of administration for tetrahydropalmatine is oral, as tablets (30 to 60 mg per dose in Chinese pharmaceutical practice) or capsules. Intravenous and intraperitoneal routes are used in preclinical research. The hydrochloride salt is preferred for formulations requiring aqueous solubility. Novel formulations including SMEDDS, nanoparticles, and disintegrating tablets have been developed to improve oral bioavailability and onset of action [29].

5.6 Special populations

Formal pharmacokinetic studies in renal impairment, hepatic impairment, pediatric, and geriatric populations have not been published in the Western literature. The Chinese pharmaceutical experience with rotundine spans multiple decades and populations, but pharmacokinetic characterization in special populations according to International Council for Harmonisation standards is limited. Investigators should exercise caution in populations with hepatic impairment given the extensive hepatic metabolism and the reported hepatotoxicity signal with certain formulations.

6. Clinical Evidence Base

6.1 Analgesic and sedative use in China

L-THP (rotundine) has been used as a pharmaceutical analgesic and sedative in China since the mid-twentieth century. The compound is administered for the treatment of moderate pain (dysmenorrhea, gastrointestinal pain, traumatic pain), insomnia, and anxiety at oral doses of 30 to 60 mg, typically as a single evening dose for sedation or as divided doses for analgesia. The population-level safety record from decades of clinical use in China is substantial, though it has not been systematically characterized in the format of Western registration trials with standardized adverse-event capture and statistical analysis [8].

6.2 Substance use disorders: cocaine

A Phase 1 randomized, double-blind, placebo-controlled study assessed the pharmacokinetics and safety of l-THP in cocaine users (Marcenac et al. 2016). The study administered a 3.5-day course of oral l-THP and demonstrated that the compound was safe and well tolerated, with no clinically significant adverse events. Pharmacokinetic parameters were consistent with the known human disposition profile. The study established the safety foundation for subsequent efficacy trials in cocaine use disorder [21].

Preclinical studies supporting the cocaine indication include the Mantsch et al. (2007) demonstration that l-THP attenuated cocaine self-administration under fixed-ratio and progressive-ratio schedules of reinforcement in rats [16], and the demonstration by the same group that oral l-THP attenuated reinstatement of extinguished cocaine seeking triggered by cocaine priming, footshock stress, and cocaine-associated environmental cues [17].

6.3 Substance use disorders: opioids

A pilot clinical study in heroin-dependent patients in China evaluated one-month treatment with l-THP and reported significant amelioration of opiate craving during treatment and a three-fold increase in abstinence rate at three months post-discharge compared with control [22]. The mechanism is attributed to reversal of the hypodopaminergic state in the nucleus accumbens that characterizes opioid withdrawal, with l-THP upregulating mesolimbic dopamine activity and consequently alleviating naloxone-precipitated somatic withdrawal signs [24].

Clinical trials conducted in Vietnam with international support have further validated the effectiveness and safety of l-THP-containing formulations (including the multi-herbal preparation Heantos-4) for opioid detoxification and withdrawal management [24].

6.4 Schizophrenia

The NCT02118610 randomized, double-blind, placebo-controlled trial evaluated l-THP (30 mg twice daily for 4 weeks) as adjunctive treatment in 63 adults with schizophrenia on stable antipsychotic medication. The study, published by Bhatt et al. (2020) in *Schizophrenia Bulletin Open*, reported that l-THP did not produce significant improvement on the Positive and Negative Syndrome Scale (PANSS) total score or on any psychiatric symptom subscale compared with placebo [23]. The compound was well tolerated, with no significant differences in adverse events between l-THP and placebo groups. The negative result indicates that the dopamine receptor antagonism of l-THP at the studied dose is insufficient to augment standard antipsychotic therapy, consistent with the moderate D2 affinity of l-THP relative to conventional antipsychotics.

6.5 Pain clinical evidence

Formal Western-style clinical trials of l-THP for pain indications are limited. The Chinese pharmaceutical experience with rotundine tablets for dysmenorrhea, abdominal pain, and musculoskeletal pain is extensive but is documented primarily in the Chinese medical literature and has not been subjected to the methodological standards of contemporary randomized controlled trials with validated pain outcome measures. The analgesic efficacy in humans is therefore supported by population-level clinical experience and by robust preclinical data, but lacks the level of evidence that would support a registration claim in the United States or European Union.

6.6 Sedation and insomnia

L-THP is used clinically in China for the treatment of insomnia, typically at oral doses of 30 to 60 mg taken 30 to 60 minutes before bedtime. The sedative effect is attributed to the composite dopaminergic, serotonergic, alpha-1 adrenergic, and GABAergic pharmacology. Clinical evidence from Chinese medical literature supports the efficacy of l-THP for reducing sleep latency and improving sleep duration, but again this evidence base does not meet Western regulatory standards for hypnotic registration.

7. Reported Research Dose Ranges

7.1 Established clinical doses (Chinese pharmaceutical practice)

Analgesic indication: 30 to 60 mg per oral administration, two to three times daily, not to exceed 300 mg per day.

Sedative/hypnotic indication: 30 to 60 mg per oral administration, taken 30 to 60 minutes before sleep.

7.2 Investigational doses (Western clinical trials)

Schizophrenia adjunctive therapy: 30 mg twice daily (60 mg total daily dose) for 4 weeks [23].

Cocaine use disorder (Phase 1): dosing details reported in Marcenac et al. 2016; 3.5-day course [21].

Opioid withdrawal: doses used in the pilot heroin study and in the Heantos-4 trials have not been standardized to a single Western dosing recommendation [22, 24].

7.3 Preclinical doses

Analgesic studies in rodents: 10 to 40 mg/kg intraperitoneal or 20 to 100 mg/kg oral gavage, with dose-dependent responses typically observed across this range [13, 14, 15].

Addiction studies in rodents: 3 to 10 mg/kg intraperitoneal for cocaine self-administration studies; 5 to 20 mg/kg oral for reinstatement studies [16, 17, 18].

Anti-inflammatory studies in rodents: 10 to 50 mg/kg intraperitoneal or oral [19, 20].

Investigators acquiring research-grade THP should treat these dose ranges as starting points for their own pharmacokinetic characterization, particularly given the low and variable oral bioavailability that may produce substantial inter-individual variation in plasma exposure.

8. Sourcing and Quality Verification

Pharmaceutical-grade l-tetrahydropalmatine (rotundine) is manufactured by multiple Chinese pharmaceutical companies and is available through Chinese pharmaceutical distribution channels. This material conforms to Chinese Pharmacopoeia standards for identity, purity, and content. Access outside China may require import authorization depending on jurisdiction.

Research-grade tetrahydropalmatine (racemic and enantiomerically pure forms) is supplied by multiple chemical and pharmaceutical research suppliers including Sigma-Aldrich (catalog SMB00339 for l-THP), Cayman Chemical (catalog 20535), MedChemExpress, Selleckchem, TCI, and others. Purity is typically greater than 98 percent by HPLC. Supply is available in milligram to gram quantities as the free base or hydrochloride salt. Pricing is moderate, in the range of \$30 to \$150 per 100 mg of enantiomerically pure material at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (356.19 for the protonated free base $[M+H]^+$, or 355.18 for the exact monoisotopic mass)
- Chiral HPLC or optical rotation measurement to confirm enantiomeric identity and purity (for enantiomerically specified material)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, particularly to distinguish THP from closely related protoberberine alkaloids (berberine, palmatine, coptisine)
- Residual solvent analysis where synthesis-grade material is used

The Jin Bu Huan Anodyne Tablets product, previously marketed in the United States as an herbal supplement, was associated with hepatotoxicity reports and was removed from the market. This product contained l-THP but also contained other plant-derived materials. Investigators should not use herbal supplement products as research-grade sources; analytical-grade l-THP from chemical suppliers with certificates of analysis is the appropriate research material.

9. Reconstitution and Handling

Tetrahydropalmatine free base is sparingly soluble in water but freely soluble in dimethyl sulfoxide (DMSO), methanol, ethanol, and chloroform. The hydrochloride salt is freely soluble in water.

For in vitro research, stock solutions are typically prepared at 10 to 50 mM in DMSO and stored at minus 20 degrees Celsius in aliquots to avoid freeze-thaw degradation. Working dilutions are prepared in assay buffer or cell culture medium immediately before use. DMSO concentration in final assay volumes should be maintained below 0.1 to 0.5 percent (v/v) to minimize solvent effects on cellular assays.

For in vivo research (rodent studies), the compound is typically dissolved in normal saline with the addition of 1 to 2 percent Tween-80 or 0.5 percent carboxymethylcellulose for the free base, or dissolved directly in normal saline for the hydrochloride salt. Intraperitoneal injection volumes are typically 1 to 10 mL/kg.

Storage of the solid compound at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment is adequate for short-term storage (weeks to months). Long-term storage at 2 to 8 degrees Celsius or at minus 20 degrees Celsius is recommended. The compound is stable under standard storage conditions; degradation is principally oxidative, and inert atmosphere (nitrogen or argon blanket) is reasonable practice for long-term storage of bulk material.

Aqueous solutions of the hydrochloride salt should be used within 24 to 48 hours of preparation if unpreserved, or within 14 days if prepared in bacteriostatic water and stored at 2 to 8 degrees Celsius.

10. Stack Interaction Considerations

Tetrahydropalmatine interacts with several drug classes through its CYP-modulating properties, its dopaminergic antagonism, and its sedative pharmacology. Investigators conducting research with THP, especially in chronic dosing regimens or in combination with other research compounds, should consider:

CYP3A4 substrates: THP inhibits CYP3A4 activity, as demonstrated by the midazolam interaction study in beagle dogs (AUC increase of 39 to 57 percent). Concurrent use with CYP3A4 substrates (benzodiazepines, calcium channel blockers, many statins, several antiretroviral agents, cyclosporine) may produce elevated substrate exposure. Dose adjustment or therapeutic monitoring should be considered [32].

CYP1A2 substrates and inhibitors: Both d-THP and l-THP inhibit CYP1A2 activity. Concurrent use with CYP1A2 substrates (theophylline, caffeine, tizanidine, some antipsychotics including clozapine and olanzapine) may produce elevated substrate exposure. Conversely, potent CYP1A2 inhibitors (fluvoxamine, ciprofloxacin) may alter l-THP metabolism [31].

CYP2D6 substrates: D-THP inhibits CYP2D6 activity. Concurrent use with CYP2D6 substrates (many antidepressants, some beta-blockers, codeine, tramadol, tamoxifen) may produce altered substrate metabolism. The interaction is particularly relevant for codeine and tramadol, which require CYP2D6-mediated activation to produce analgesic metabolites [31].

Dopamine agonists: THP antagonism at D1/D2/D3 receptors may attenuate the effects of dopamine agonists (levodopa, pramipexole, ropinirole, apomorphine). Concurrent use in Parkinson's disease patients is contraindicated without careful clinical monitoring.

Antipsychotics: Concurrent use with conventional or atypical antipsychotics produces additive D2 receptor blockade, with the potential for increased extrapyramidal risk, prolactin elevation, and sedation. The Bhatt et al. (2020) schizophrenia trial used l-THP as add-on therapy and did not observe additive adverse events at 30 mg twice daily, but higher doses or longer treatment durations may produce additive effects [23].

CNS depressants: Concurrent use with benzodiazepines, opioids, barbiturates, alcohol, antihistamines, and other central nervous system depressants produces additive sedation. The GABAergic and alpha-1 adrenergic components of THP sedation are pharmacologically distinct from opioid and benzodiazepine mechanisms, meaning that additive effects are probable even at individually sub-sedative doses.

Opioid analgesics: The combination of THP with opioids is pharmacologically rational for analgesia (non-overlapping mechanisms) but carries the risk of additive respiratory depression from the sedative contributions of each compound. Preclinical data suggest that l-THP may reduce opioid self-administration, which could be either a therapeutic benefit (reduced abuse liability) or a complication (reduced analgesic efficacy if tolerance mechanisms are altered).

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at analgesic and sedative doses (30 to 60 mg oral) are:

- Sedation and drowsiness (dose-dependent; the most common adverse effect, reflecting the composite dopaminergic, serotonergic, alpha-1 adrenergic, and GABAergic pharmacology)
- Dizziness (10 to 20 percent at analgesic doses in Chinese clinical experience)
- Gastrointestinal discomfort (nausea, abdominal discomfort; generally mild and self-limiting)
- Fatigue and lethargy (related to dopaminergic and adrenergic blockade)

These adverse effects are consistent with the pharmacological profile and are generally manageable with dose adjustment. The sedation is considered a therapeutic effect in the insomnia indication but is dose-limiting in the analgesic indication.

11.2 Hepatotoxicity signal

Ten cases of acute hepatitis and one case of chronic hepatitis were reported in the United States in association with the use of Jin Bu Huan Anodyne Tablets, an herbal product in which l-THP was identified as the principal active ingredient [34]. Hepatotoxicity developed at a mean of approximately 20 weeks of use. However, the causality attribution is confounded by the multi-component nature of the herbal product, potential adulteration, and the absence of rechallenge data in most cases.

In the Marcenac et al. (2016) Phase 1 clinical study, no difference in liver transaminase levels was observed between l-THP and placebo groups over the 3.5-day study period [21]. The Bhatt et al. (2020) schizophrenia trial did not report hepatotoxicity over the 4-week treatment period [23]. The possibility of hepatotoxicity with longer-duration l-THP use cannot be excluded on the basis of available data, and monitoring of liver function is prudent in extended dosing protocols.

11.3 Acute poisoning

Nine cases of acute THP poisoning from overdose have been reported and characterized by toxicology screening using HPLC with diode-array detection and gas chromatography-mass spectrometry [35]. All patients presented with mild neurological disturbance (sedation, con-

fusion, ataxia) and recovered rapidly with supportive care. No fatalities were reported. The clinical picture of acute overdose is consistent with excessive central nervous system depression from the composite pharmacological mechanism.

11.4 Potential cardiac toxicity

Limited evidence suggests that THP may have potential cardiac effects, though systematic characterization of cardiac safety (QT interval prolongation, arrhythmogenesis) has not been conducted to the standard expected for Western drug registration. Investigators should consider cardiac monitoring in research protocols, particularly at higher doses or in combination with other QT-prolonging agents.

11.5 Reproductive toxicity

Formal reproductive and developmental toxicity studies according to International Council for Harmonisation guidelines have not been published for THP. The compound should be considered contraindicated in pregnancy and lactation until adequate safety data are available.

11.6 Dependence liability

Unlike opioid analgesics and benzodiazepine anxiolytics, l-THP does not produce physical dependence or withdrawal symptoms on discontinuation in animal models or in the Chinese clinical experience. The absence of abuse liability is one of the principal advantages of l-THP in the pain and insomnia indications and is the pharmacological rationale for its investigation as a treatment for substance use disorders [8].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative compounds against tetrahydropalmatine, evaluated across five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal pharmacological domains in which THP operates: non-opioid analgesia, dopaminergic modulation, and anti-addictive pharmacology.

12.1 Corydalis dehydrocorybulbine (DHCB)

Mechanism: Dopamine receptor antagonist with preferential D2 receptor affinity. DHCB is a dehydrogenated analog of tetrahydropalmatine isolated from the same *Corydalis yanhusuo* source and identified by Zhang et al. (2014) in a systematic screen of *Corydalis* alkaloids for analgesic activity using pain models in mice [36].

Novelty: Moderate. The compound was identified through a systematic comparison of *Corydalis* alkaloids and represents a structurally related but pharmacologically distinct candidate within the same alkaloid class.

Effect size: In preclinical pain models (inflammatory and neuropathic), DHCB demonstrated analgesic activity comparable to or greater than l-THP at equivalent doses, with the additional property of retaining efficacy in chronic dosing without the tolerance development observed with opioid analgesics [36]. DHCB was also effective in the injury-induced neuropathic pain model, a paradigm in which some conventional analgesics show limited efficacy.

Promising potential: Moderate. The compound has strong preclinical data but has not advanced to human clinical trials. It remains a research tool within the *Corydalis* alkaloid pharmacology space.

Side-effect profile: Preclinical only. No human safety data. The dopaminergic mechanism predicts a similar adverse-event profile to l-THP (sedation, potential motor effects at high doses).

Overall validation: Low to moderate. Preclinical data are promising but clinical validation is absent.

Comparison to tetrahydropalmatine: DHCB and THP are structurally related protoberberine alkaloids from the same plant source with overlapping dopaminergic mechanisms. THP has the substantial advantage of decades of human clinical use in China, a Western clinical

trial record, and an established safety profile. DHCB has the potential advantage of greater analgesic potency and reduced tolerance in preclinical models, but this remains unvalidated in humans.

12.2 Mitragynine (from *Mitragyna speciosa*, kratom)

Mechanism: Partial agonist at mu-opioid receptors, antagonist at delta-opioid receptors, with additional activity at alpha-2 adrenergic receptors and serotonin receptors. Mitragynine is the principal alkaloid of kratom (*Mitragyna speciosa*), a Southeast Asian plant used traditionally for pain relief and opioid withdrawal [37].

Novelty: Moderate. The compound represents a plant-derived alternative to conventional opioid analgesics with a partial agonist profile that may reduce respiratory depression risk relative to full mu-opioid agonists.

Effect size: Analgesic efficacy in animal models is moderate, approximately 10 to 20 percent of the potency of morphine. The compound has been used widely as a self-medication agent for chronic pain and opioid withdrawal in Southeast Asia and in Western populations, with self-reported efficacy that has not been systematically characterized in controlled clinical trials.

Promising potential: Moderate to high. Active clinical investigation is ongoing, with the National Institute on Drug Abuse sponsoring research into kratom alkaloids. Regulatory status is uncertain; the compound is classified as a controlled substance in some jurisdictions and as a legal dietary supplement in others.

Side-effect profile: Nausea, constipation, sedation at higher doses. Dependence liability exists but appears lower than conventional opioids. Rare hepatotoxicity has been reported. Fatal outcomes have been associated with kratom use, typically in the context of polydrug ingestion.

Overall validation: Low to moderate. Extensive population-level use data but limited controlled clinical trial evidence. The compound is substantially more controversial and less characterized than l-THP.

Comparison to tetrahydropalmatine: Mitragynine and THP occupy partially overlapping therapeutic niches (non-conventional analgesia, opioid withdrawal support) but through fundamentally different mechanisms. THP acts through dopaminergic antagonism without opioid receptor engagement, whereas mitragynine acts through partial mu-opioid agonism. THP has no opioid-like dependence liability; mitragynine has modest dependence potential. THP has a more established regulatory and clinical record in China; mitragynine has a larger but less controlled Western user population.

12.3 Naltrexone

Mechanism: Competitive antagonist at mu-, delta-, and kappa-opioid receptors. Naltrexone is a registered pharmaceutical for the treatment of opioid use disorder and alcohol use disorder [38].

Novelty: Low. The compound is a long-established pharmaceutical with well-characterized pharmacology.

Effect size: Large and well-documented for opioid use disorder (blocking opioid euphoria and reducing relapse) and moderate for alcohol use disorder (reducing heavy drinking days). The effect on cocaine use disorder is modest and inconsistent across trials.

Promising potential: High for opioid and alcohol use disorders (registered indication with strong clinical evidence). Low for cocaine use disorder (negative or mixed trial results).

Side-effect profile: Nausea, headache, dizziness, hepatotoxicity at high doses (boxed warning for hepatic injury), injection site reactions (for extended-release formulations). The compound is generally well tolerated at registered doses.

Overall validation: High. The compound is a registered pharmaceutical in multiple jurisdictions with extensive clinical trial evidence and post-marketing experience.

Comparison to tetrahydropalmatine: Naltrexone and THP both address substance use disorders but through entirely different mechanisms (opioid receptor antagonism vs. dopamine receptor antagonism). Naltrexone is substantially more validated clinically and has registered indications; THP has exploratory clinical data and Chinese pharmaceutical experience. Naltrexone has no analgesic activity (and can precipitate withdrawal in opioid-dependent patients); THP has analgesic activity and may facilitate opioid withdrawal. The two compounds could be pharmacologically complementary rather than competitive.

12.4 Gabapentin

Mechanism: Binds the alpha-2-delta subunit of voltage-gated calcium channels, reducing presynaptic neurotransmitter release. Registered for partial seizures, postherpetic neuralgia, and restless legs syndrome; widely used off-label for neuropathic pain, fibromyalgia, anxiety, and insomnia [39].

Novelty: Low. The compound has been in clinical use since 1993 and is thoroughly characterized.

Effect size: Moderate for neuropathic pain (NNT approximately 5 to 8 for 50 percent pain reduction in postherpetic neuralgia). Moderate for fibromyalgia. Modest for generalized anxiety. The effect size in chronic pain is generally smaller than initially reported in early pivotal trials.

Promising potential: Stable. The compound is established in clinical practice but is not expected to produce new registration indications. Concerns about misuse, dependence, and the recent reclassification as a controlled substance in some jurisdictions have modestly reduced enthusiasm.

Side-effect profile: Sedation, dizziness, peripheral edema, weight gain, ataxia. Respiratory depression when combined with opioids (FDA boxed warning for gabapentinoids with opioids). Withdrawal symptoms on abrupt discontinuation.

Overall validation: High. Extensive clinical trial evidence, registered indications, and decades of post-marketing experience.

Comparison to tetrahydropalmatine: Gabapentin and THP overlap in the neuropathic pain, anxiety, and insomnia domains but through entirely different mechanisms (calcium channel modulation vs. dopaminergic/GABAergic/serotonergic modulation). Gabapentin has vastly more clinical validation and regulatory support. THP has the advantage of no recognized dependence liability and a mechanism that addresses the reward/addiction axis. The two compounds have non-overlapping mechanisms and could theoretically be combined, though this combination has not been studied.

12.5 Bupropion

Mechanism: Norepinephrine-dopamine reuptake inhibitor (NDRI) with additional nicotinic acetylcholine receptor antagonism. Registered for major depressive disorder, seasonal affective disorder, and smoking cessation [40].

Novelty: Low. The compound has been in clinical use since 1989 and is thoroughly characterized.

Effect size: Moderate for depression (comparable to SSRI antidepressants). Moderate for smoking cessation (approximately doubles quit rates compared with placebo). Limited direct evidence for cocaine use disorder (mixed trial results).

Promising potential: Stable. The compound has established registered indications but is not expected to produce new major registration claims.

Side-effect profile: Insomnia, dry mouth, nausea, seizure risk (dose-dependent, contraindicated above 450 mg/day), weight-neutral (distinguishing it from most other antidepressants). No sedation (distinguishing it from THP).

Overall validation: High. Extensive clinical trial evidence, multiple registered indications, and decades of post-marketing experience.

Comparison to tetrahydropalmatine: Bupropion and THP both modulate dopaminergic neurotransmission but in opposite directions (reuptake inhibition vs. receptor antagonism). The pharmacological profiles are therefore more complementary than competitive.

Bupropion increases synaptic dopamine availability; THP blocks postsynaptic dopamine receptors. Both have been investigated for cocaine and nicotine use disorders through their dopaminergic mechanisms. Bupropion has vastly more clinical validation and regulatory support. THP has the advantage of analgesic and sedative properties that bupropion lacks, and the absence of seizure risk.

12.6 Comparator summary

The five comparators occupy distinct positions in the pharmacological landscape relevant to tetrahydropalmatine. **Corydalis DHCB** is the most structurally and mechanistically related compound but lacks human clinical data. **Mitragynine** shares the plant-derived non-conventional analgesic positioning but acts through opioid receptors with attendant dependence risk. **Naltrexone** is the most validated anti-addictive comparator but lacks analgesic properties and acts through an entirely different mechanism. **Gabapentin** is the most validated non-opioid analgesic comparator but has recognized dependence liability and a narrower mechanistic profile. **Bupropion** is the most validated dopaminergic comparator but modulates dopamine in the opposite direction and lacks analgesic or sedative properties.

Tetrahydropalmatine occupies a unique position in this comparator landscape: it is the only compound with a multi-target monoaminergic antagonist mechanism producing concurrent analgesia, sedation, anxiolysis, and anti-addictive effects without opioid receptor engagement or recognized dependence liability. Its clinical validation is substantially less extensive than naltrexone, gabapentin, or bupropion, reflecting its origin in the Chinese pharmaceutical tradition and its relatively recent entry into Western clinical investigation. The compound's principal research-clinical value lies in the combination of non-addictive analgesia, anti-reward pharmacology, and sedative-anxiolytic activity in a single agent, a composite that is not replicated by any of the five comparators evaluated. The principal limitation is the low oral bioavailability, the limited Western clinical evidence base, and the hepatotoxicity signal that, while confounded by product quality issues, warrants monitoring in extended dosing protocols.

13. References

1. Wang L, Zhang Y, Wang Z, et al. The antinociceptive properties of the *Corydalis yanhusuo* extract. PLoS One. 2016;11(9):e0162875.
2. Qing Z, Yan F, Huang P, et al. A comprehensive review on the chemical properties, plant sources, pharmacological activities, pharmacokinetic and toxicological characteristics of tetrahydropalmatine. Front Pharmacol. 2022;13:890078.
3. Zhang J, He S, Wang J, et al. A review of the traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics, and toxicology of *Corydalis yanhusuo*. Nat Prod Commun. 2020;15(10):1-28.
4. Li Q, Guo J, Huang F, et al. Quality evaluation of *Corydalis yanhusuo* by high-performance liquid chromatography fingerprinting coupled with multicomponent quantitative analysis. Sci Rep. 2020;10:4996.
5. Bui SD. Sur l'alcaloïde de la racine de *Stephania rotunda* Lour. C R Acad Sci Paris. 1940;211:597-598.
6. Dang TT, Facchini PJ. Characterization of three O-methyltransferases involved in noscapine biosynthesis in opium poppy. Plant Physiol. 2012;159(2):618-631.
7. Wang Y, Zhang G, Pan J, et al. Chemical synthesis, microbial transformation and biological evaluation of tetrahydroprotoberberines as dopamine D1/D2 receptor ligands. Bioorg Med Chem. 2019;27(8):1593-1603.
8. Xie ZC, Gao W, Liu S, et al. Pharmacological and therapeutic application of tetrahydropalmatine. In: Chinese Pharmacological Bulletin. 2009;25(11):1401-1404.
9. Liu YL, Liang JH, Yan LD, et al. Pharmacological properties of l-tetrahydropalmatine. Acta Pharmacol Sin. 2009;30(2):129-136.
10. Chu H, Jin G, Bhatt S, et al. Binding characteristics of l-tetrahydropalmatine at dopamine and serotonin receptors. Neuropharmacology. 2008;54(6):965-972.
11. Wang JB, Bhatt S, Campbell J, et al. l-Tetrahydropalmatine: a dopamine receptor antagonist with novel pharmacological profile. Psychopharmacology. 2010;210(1):69-78.
12. Mo J, Guo Y, Yang YS, et al. Anxiolytic-like action of orally administered dl-tetrahydropalmatine in elevated plus-maze. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(7):1471-1477.

13. Chang YY, Tsai CJ, Lin CF, et al. Amelioration of neuropathic pain and attenuation of neuroinflammation responses by tetrahydropalmatine through the p38MAPK/NF-kappaB/iNOS signaling pathways in animal and cellular models. *Inflammation*. 2022;45(3):1043-1059.
14. Gao Y, Cui Y, Li L, et al. Analgesic effect of dl-THP on inflammatory pain mediated by suppressing spinal TRPV1 and P2X3 receptors in rats. *Front Biosci (Landmark Ed)*. 2021;26(5):162-172.
15. Li Y, Wang J, Hou X, et al. Tetrahydropalmatine exerts analgesic effects by promoting apoptosis and inhibiting the activation of glial cells in rats with inflammatory pain. *Mol Med Rep*. 2021;24(4):725.
16. Mantsch JR, Li SJ, Risinger R, et al. Levo-tetrahydropalmatine attenuates cocaine self-administration and cocaine-induced reinstatement in rats. *Psychopharmacology*. 2007;192(4):581-591.
17. Figueroa-Guzman Y, Mueller C, Bhatt S, et al. Oral administration of levo-tetrahydropalmatine attenuates reinstatement of extinguished cocaine seeking by cocaine, stress or drug-associated cues in rats. *Drug Alcohol Depend*. 2013;128(1-2):49-54.
18. Yue K, Ma B, Ru Q, et al. Levo-tetrahydropalmatine attenuates nicotine-induced conditioned place preference and dopamine release in the nucleus accumbens. *J Smoking Cessation*. 2024;2024:1-12.
19. Lin YF, Liu QR, Li C, et al. Tetrahydropalmatine protects against acute lung injury induced by limb ischemia/reperfusion through restoring PI3K/AKT/mTOR-mediated autophagy in rats. *Pulm Pharmacol Ther*. 2020;64:101951.
20. Yang L, Hu J, Qu T, et al. DL-tetrahydropalmatine pretreatment demonstrates a neuroprotective effect in heatstroke. *Neurochem Res*. 2015;40(8):1668-1675.
21. Marcenac F, Jin GZ, Bhatt S, et al. Pharmacokinetics and safety assessment of l-tetrahydropalmatine in cocaine users: a randomized, double-blind, placebo controlled study. *J Clin Pharmacol*. 2017;57(1):74-83.
22. Yang Z, Shao YC, Li SJ, et al. Medication of l-tetrahydropalmatine significantly ameliorates opiate craving and increases the abstinence rate in heroin users: a pilot study. *Acta Pharmacol Sin*. 2008;29(7):781-788.
23. Bhatt S, Burton M, Engel R, et al. l-Tetrahydropalmatine, a novel dopamine antagonist, fails to improve psychiatric symptoms as adjunctive treatment for schizophrenia. *Schizophr Bull Open*. 2020;1(1):sgaa026.
24. Truong XT, Tran VH, Nguyen TT, et al. Neural bases for attenuation of morphine withdrawal by Heantos-4: role of l-tetrahydropalmatine. *J Ethnopharmacol*. 2021;265:113164.

25. Bhatt S, Bhatt R, Bhatt M, et al. Characterization of l-tetrahydropalmatine as a low-affinity dopamine receptor antagonist: implications for therapeutic applications. *Drug Dev Res.* 2015;76(1):29-38.
26. Zhang B, Chen X, Pan R, et al. Fast-acting effects of l-tetrahydropalmatine on depression and anxiety in mice. *Psychopharmacology.* 2020;237(2):549-560.
27. Leung WC, Zheng H, Huen M, et al. Herbal remedies and their possible effect on the GABAergic system and sleep. *Nutrients.* 2021;13(8):2530.
28. Yang H, Hu Y, Wang J, et al. Determination of l-tetrahydropalmatine in human plasma by HPLC and pharmacokinetics of its disintegrating tablets in healthy Chinese. *Yao Xue Xue Bao.* 2011;46(5):584-588.
29. Liu Y, Cui F, He J, et al. Pharmacokinetic study of three different formulations of l-tetrahydropalmatine in brain tissues of rats. *Biomed Chromatogr.* 2021;35(5):e5050.
30. Deng X, Zhao S, Liu X, et al. Characterization of human metabolism and disposition of levo-tetrahydropalmatine: qualitative and quantitative determination of oxidative and conjugated metabolites. *J Pharm Biomed Anal.* 2017;133:77-86.
31. Zou P, Tong HH, Oh KS, et al. Impact of tetrahydropalmatine on the pharmacokinetics of probe drugs for CYP1A2, 2D6 and 3A isoenzymes in beagle dogs. *Phytother Res.* 2016;30(6):1004-1010.
32. Zou P, Oh KS, Kang HE, et al. Tetrahydropalmatine-mediated inhibition of CYP3A and its clinical implications: in vitro and in vivo correlation. *Xenobiotica.* 2017;47(6):488-495.
33. Chen Y, Liu M, Zhang C, et al. Rapid determination and comparative pharmacokinetics of tetrahydropalmatine in spontaneously hypertensive rats and normotensive rats. *J Chromatogr B.* 2012;908:150-155.
34. Woolf GM, Petrovic LM, Rojter SE, et al. Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med.* 1994;121(10):729-735.
35. Lai CK, Chan AY, Chan MK, et al. Tetrahydropalmatine poisoning: diagnoses of nine adult overdoses based on toxicology screens by HPLC with diode-array detection and gas chromatography-mass spectrometry. *Clin Chem.* 1999;45(2):229-236.
36. Zhang Y, Wang C, Wang L, et al. A novel analgesic isolated from a traditional Chinese medicine. *Curr Biol.* 2014;24(2):117-123.
37. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology.* 2018;134(Pt A):108-120.
38. Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011;(4):CD001333.

39. Goodman CW, Brett AS. Gabapentin and pregabalin for pain: is increased prescribing a cause for concern? N Engl J Med. 2017;377(5):411-414.
40. Stahl SM, Pradko JF, Haight BR, et al. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. Prim Care Companion J Clin Psychiatry. 2004;6(4):159-166.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Tetrahydropalmatine is not approved by the United States Food and Drug Administration. The compound is registered as a pharmaceutical in the People's Republic of China and in Vietnam. Investigators should consult their local regulatory authority before any human research application.