

RESEARCH MONOGRAPH . COMPOUND PROFILE

Paraxanthine

The principal dimethylxanthine metabolite of caffeine in humans, distinguished from the parent compound and from other methylxanthines by selective inhibition of cGMP-preferring phosphodiesterase 9, potentiation of nitric oxide signaling, ryanodine receptor channel activation, and a favorable safety profile relative to caffeine.

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ABSTRACT

Paraxanthine (1,7-dimethylxanthine) is the primary metabolite of caffeine in humans, accounting for approximately 80 percent of caffeine biotransformation through hepatic cytochrome P450 1A2 (CYP1A2) catalyzed N3-demethylation. Although structurally an isomer of the naturally occurring dimethylxanthines theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine), paraxanthine is not produced by plants and is encountered in human plasma exclusively as a product of caffeine metabolism. The compound has received escalating research attention since the mid-2000s as a pharmacologically distinct entity rather than a mere intermediate metabolite, with a mechanism of action profile that diverges meaningfully from caffeine at several molecular targets.

The principal pharmacological activities of paraxanthine are competitive antagonism at adenosine A1 and A2A receptors (with binding affinities comparable to or modestly greater than caffeine), selective inhibition of the cGMP-preferring phosphodiesterase PDE9 (an activity not shared by caffeine, theophylline, or theobromine), potentiation of nitric oxide neurotransmission (a unique property among the naturally occurring methylxanthines), and activation of ryanodine receptor calcium release channels (the mechanism underlying its neuroprotective activity in dopaminergic cell models). The composite pharmacology produces psychostimulant, procognitive, neuroprotective, lipolytic, and ergogenic effects that are quantitatively and qualitatively distinguishable from those of caffeine in both preclinical and clinical studies.

Pharmacokinetically, paraxanthine is generated in the liver from caffeine with a formation half-life determined by CYP1A2 activity and reaches plasma concentrations that exceed those of the parent compound approximately 8 to 10 hours after caffeine ingestion. When administered exogenously as pure paraxanthine, the compound exhibits an elimination half-life of approximately 3.1 hours (shorter than caffeine at 4.1 hours, theophylline at 6.2 hours, and theobromine at 7.2 hours), rapid oral absorption, and dose-proportional pharmacokinetics across the studied range of 100 to 400 mg. The shorter half-life contributes to a cleaner offset of stimulant effects and reduced sleep disruption relative to caffeine at equimolar doses.

Clinical evidence from double-blind, placebo-controlled crossover trials demonstrates that acute oral paraxanthine at 100 to 200 mg improves sustained attention, working memory, executive function, reaction time, and psychomotor vigilance in healthy adults, with effects comparable to or exceeding those of caffeine on several cognitive endpoints and with fewer reported adverse events. A 2024 study demonstrated superior cognitive maintenance after a 10-kilometer run compared to caffeine, with caffeine-treated subjects committing 31 percent more errors while paraxanthine-treated subjects improved correct responses by approximately 6.8 percent. Preclinical studies in rodents have demonstrated that paraxanthine supplementation increases muscle mass by 14 to 41 percent, forelimb grip strength by 17 percent, and treadmill endurance by 39 percent relative to control. Paraxanthine has also been shown to enhance brain-derived neurotrophic factor (BDNF) levels, elevate hippocampal acetylcholine and dopamine, and provide neuroprotection against MPTP-induced dopaminergic cell death through ryanodine receptor channel activation.

The safety profile of paraxanthine is favorable relative to caffeine. In 90-day repeat-dose oral toxicity studies in rats, the no-observed-adverse-effect level (NOAEL) for paraxanthine was established at 185 mg/kg body weight compared to 150 mg/kg for caffeine; mortality was observed in two rats receiving caffeine at 185 mg/kg but in none receiving paraxanthine at the same dose. The acute oral LD₅₀ in rats is 829.20 mg/kg. In vitro genotoxicity and mutagenicity studies are negative. In human clinical studies, acute and 7-day daily ingestion of paraxanthine at doses up to 300 mg has not been associated with clinically significant adverse events, changes in blood pressure, or anxiogenic effects at the magnitude observed with equivalent caffeine doses. The ingredient has achieved self-affirmed Generally Recognized as Safe (GRAS) status for use in food and beverages in the United States at levels up to 300 mg per serving. This monograph reviews the chemistry, synthesis, and structural relationships of paraxanthine; the multi-target mechanism of action; the comprehensive pharmacokinetic record; preclinical pharmacology across cognitive, neuroprotective, ergogenic, and metabolic endpoints; the clinical evidence base; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events and safety; and a comparative assessment of five methylxanthine and stimulant alternatives against paraxanthine on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Recommended International Nonproprietary Name: Paraxanthine (not formally assigned by the World Health Organization; the compound is not a registered pharmaceutical in any jurisdiction).

Chemical name: 1,7-Dimethylxanthine.

Common synonyms: 1,7-Dimethyl-3H-purine-2,6-dione; 1,7-dimethyl-1H-purine-2,6(3H,7H)-dione.

Trade names and branded ingredients: enfinity (Ingenious Ingredients, ING2; the principal commercial source of synthetic paraxanthine for dietary supplement and food applications).

Chemical Abstracts Service registry number: 611-59-6.

PubChem Compound Identifier: CID 4687.

Human Metabolome Database identifier: HMDB0001860.

DrugBank identifier: DBMET00223.

International Union of Pure and Applied Chemistry name: 1,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione.

1.2 Structural class and chemistry

Paraxanthine is a dimethylxanthine, a member of the purine alkaloid family that includes caffeine (1,3,7-trimethylxanthine), theophylline (1,3-dimethylxanthine), and theobromine (3,7-dimethylxanthine). It is the 1,7-positional isomer of the dimethylxanthine series, carrying methyl substituents at the N1 and N7 nitrogen positions of the xanthine (2,6-dioxopurine) core. The structural class places it within the broader methylxanthine family, a pharmacologically important group of naturally occurring and synthetic alkaloids that act primarily as adenosine receptor antagonists and phosphodiesterase inhibitors [1, 2].

Molecular formula: C₇H₈N₄O₂.

Exact mass: 180.0647 g/mol (monoisotopic).

Molecular weight: 180.16 g/mol.

Physical properties: White to off-white crystalline powder. Sparingly soluble in water at room temperature (approximately 1 mg/mL), freely soluble in hot water and in dimethyl sulfoxide, moderately soluble in methanol and ethanol. Melting point is approximately 352 to 354 degrees Celsius with decomposition. The compound is stable under normal storage conditions and is not hygroscopic.

InChI Key: QUNWUDVFRNGTCO-UHFFFAOYSA-N.

Structural distinction from other dimethylxanthines: The three dimethylxanthine isomers (paraxanthine, theophylline, theobromine) differ only in the positions of the two methyl groups on the xanthine ring. This positional isomerism produces substantial pharmacological divergence: paraxanthine is a selective PDE9 inhibitor and nitric oxide signaling potentiator (activities absent from the other two isomers), theophylline is a nonselective phosphodiesterase inhibitor with pronounced bronchodilatory activity, and theobromine is a mild vasodilator and diuretic with minimal central nervous system stimulant activity [3]. Paraxanthine is the only member of the dimethylxanthine series that is not produced naturally by plants; it is generated exclusively through mammalian hepatic metabolism of caffeine.

1.3 Synthesis

Paraxanthine does not occur in nature as a plant metabolite and must be obtained through chemical synthesis or through enzymatic or microbial bioconversion. The principal synthetic routes include:

Direct chemical synthesis: Selective N-methylation of xanthine at the 1- and 7-positions. The synthesis is complicated by the challenge of achieving regioselective methylation on the xanthine scaffold, which contains four nitrogen atoms with different nucleophilicities. Protecting group strategies (typically N3 protection with a removable substituent followed by sequential methylation at N1 and N7) are employed to achieve the 1,7-isomer selectively. Alternative approaches include the stepwise construction of the purine ring system from appropriately substituted

pyrimidine and imidazole precursors. The compound is characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography [4].

Enzymatic demethylation of caffeine: CYP1A2-mediated or bacterial N3-demethylation of caffeine produces paraxanthine with high regioselectivity. This biotransformation route mirrors the endogenous human metabolic pathway and has been explored as a scalable production method using recombinant CYP enzymes or whole-cell biocatalysis with caffeine-degrading microorganisms [5].

Commercial production: The enfinity branded ingredient is produced by Ingenious Ingredients through a proprietary synthesis process that yields pharmaceutical-grade paraxanthine at greater than 99 percent purity by HPLC. The commercial synthesis has been scaled to support dietary supplement and food-ingredient applications [6].

2. Abstract

Paraxanthine (1,7-dimethylxanthine; CAS 611-59-6) is the principal dimethylxanthine metabolite of caffeine in humans, generated by CYP1A2-catalyzed N3-demethylation and accounting for approximately 80 percent of total caffeine biotransformation [1, 7]. Although long studied in the context of caffeine metabolism and CYP1A2 phenotyping, paraxanthine has emerged since approximately 2006 as a pharmacologically distinct compound with a mechanism of action profile that diverges from caffeine, theophylline, and theobromine at several molecular targets.

The core pharmacology comprises four principal activities: competitive antagonism at adenosine A1 and A2A receptors (K_i approximately 21 and 32 micromolar, respectively), with binding potencies comparable to or slightly exceeding those of caffeine at both subtypes [8]; selective inhibition of the cGMP-preferring phosphodiesterase PDE9, an activity unique among the methylxanthines and hypothesized to drive glutamate and dopamine release through potentiation of the nitric oxide/cGMP signaling cascade [9, 10]; activation of ryanodine receptor calcium release channels, providing a mechanism for neuroprotection in dopaminergic neurons independent of adenosine receptor antagonism [11]; and potentiation of nitric oxide neurotransmission, an activity not shared by caffeine, theophylline, or theobromine [9].

The clinical evidence base, though more limited than that of caffeine, includes multiple double-blind, placebo-controlled trials demonstrating improvements in sustained attention, reaction time, working memory, executive function, and psychomotor vigilance in healthy adults at oral doses of 100 to 200 mg [12, 13, 14]. Preclinical pharmacology extends to neuroprotection against MPTP-induced dopaminergic cell death [11], enhancement of BDNF and hippocampal neurotransmitter levels [15], increased muscle mass and exercise performance in rodents [16], and augmented energy expenditure and lipolysis in humans [17]. The safety profile is favorable relative to caffeine, with a higher NOAEL in 90-day toxicity studies (185 versus 150 mg/kg body weight), negative genotoxicity findings, and lower anxiogenic potential at equivalent doses [6, 18].

The compound has achieved self-affirmed GRAS status in the United States for use in food and beverages at levels up to 300 mg per serving and is commercially available as the enfinity branded ingredient. It is not approved as a pharmaceutical in any jurisdiction and has no registered therapeutic indications. This monograph documents the complete pharmacological, pharmacokinetic, preclinical, clinical, safety, and comparative profile of paraxanthine as a research compound and dietary ingredient.

3. Discovery and Development History

3.1 Identification as a caffeine metabolite

Paraxanthine was first identified as a metabolite of caffeine in human urine in the mid-twentieth century through the systematic characterization of caffeine biotransformation products. The pioneering work of Cornish and Christman (1957) and subsequent studies by Callahan et al., Arnaud, and Grant established that caffeine undergoes sequential demethylation in the liver, with N3-demethylation to paraxanthine as the dominant first-step reaction in humans [1, 7]. The paraxanthine-to-caffeine plasma concentration ratio was subsequently adopted as a metabolic phenotyping probe for CYP1A2 activity, and this application dominated paraxanthine research from the 1980s through the early 2000s [19, 20].

3.2 Recognition of pharmacological distinction

The characterization of paraxanthine as a pharmacologically distinct entity (rather than a merely intermediate metabolite en route to further degradation) began with the Ferré et al. (2013) comprehensive pharmacological profiling, which demonstrated that paraxanthine exhibits a psychostimulant profile in rodents that is quantitatively and qualitatively different from caffeine [8]. The key distinctions identified were: higher locomotor activation per unit dose, selective PDE9 inhibition, unique nitric oxide signaling potentiation, and a lower anxiogenic profile at equivalent stimulant doses. This work, published in *Neuropharmacology*, established the conceptual basis for paraxanthine as a standalone research compound and potential dietary ingredient.

3.3 Neuroprotective characterization

The Bhatt et al. (2008) study in *Molecular Pharmacology* demonstrated that paraxanthine provides protection against MPTP-induced dopaminergic cell death in mouse striatal neurons through a mechanism that is independent of adenosine receptor blockade and instead depends on activation of ryanodine receptor calcium release channels [11]. This finding was significant because it identified a molecular

mechanism of action for paraxanthine that is entirely absent from caffeine and the other methylxanthines and that has direct relevance to neurodegenerative disease research.

3.4 Commercial development as a dietary ingredient

Beginning approximately 2015, Ingenious Ingredients (ING2) undertook the commercial development of synthetic paraxanthine as a dietary ingredient under the brand name enfinity. The development program included comprehensive toxicology studies (acute, subchronic, and genetic toxicity), human pharmacokinetic and safety studies, and self-affirmed GRAS determination [6]. The GRAS status was announced in November 2021 for use in energy beverages, decaffeinated coffee beverages and powders, and nutrition bars at levels up to 300 mg per serving. The first dedicated human clinical trials on exogenous paraxanthine supplementation were published beginning in 2021, establishing the dose-response for cognitive enhancement endpoints [12, 13].

3.5 Current research-commercial state

As of the monograph revision date, paraxanthine is commercially available as a dietary ingredient in the United States under self-affirmed GRAS status and is incorporated into multiple consumer supplement products (pre-workout formulations, cognitive enhancement supplements, energy beverages). It is not approved as a pharmaceutical in any jurisdiction and has no registered therapeutic indications. The research literature comprises approximately 15 to 20 dedicated publications on exogenous paraxanthine pharmacology, safety, and efficacy (as distinct from the larger body of caffeine metabolism literature in which paraxanthine features as an analyte). Active clinical investigations include a registered trial examining paraxanthine in combination with L-theanine for cognitive improvement (ClinicalTrials.gov NCT07189442) and a dose-response study of paraxanthine on cognitive and metabolic endpoints (ClinicalTrials.gov NCT06117280) [21, 22].

4. Mechanism of Action

Paraxanthine is a multi-target ligand whose pharmacological profile diverges from caffeine and the other dimethylxanthines at several molecular targets. The four principal mechanisms of action, characterized in heterologous expression systems, native tissue preparations, and behavioral models, are adenosine receptor antagonism, selective PDE9 inhibition, ryanodine receptor channel activation, and nitric oxide signaling potentiation. These activities operate at pharmacologically relevant concentrations achieved by oral doses in the 100 to 300 mg range and contribute differentially to the observed psychostimulant, procognitive, neuroprotective, and metabolic effects.

4.1 Adenosine receptor antagonism

Adenosine receptors are G-protein-coupled receptors expressed throughout the central nervous system and peripheral tissues, with four subtypes: A1, A2A, A2B, and A3. In the brain, adenosine acts as an inhibitory neuromodulator through A1 receptors (widely distributed, coupled to Gi/o, inhibiting adenylyl cyclase and neuronal excitability) and A2A receptors (concentrated in the striatum, olfactory tubercle, and nucleus accumbens, coupled to Gs, stimulating adenylyl cyclase). Adenosine accumulation during waking promotes sleep pressure and reduces arousal; antagonism of adenosine receptors is the principal mechanism of caffeine's stimulant action.

Paraxanthine binds the adenosine A1 receptor with an inhibitory constant (K_i) of approximately 21 micromolar and the A2A receptor with a K_i of approximately 32 micromolar, with higher affinity at the A2B receptor (K_i approximately 4.5 micromolar) and negligible affinity at the A3 receptor (K_i greater than 100 micromolar) [8]. These binding affinities are comparable to or slightly greater than those of caffeine at the A1 and A2A subtypes. Pharmacological studies with selective A1 and A2A receptor antagonists have established that the locomotor-activating effects of acute methylxanthine administration are primarily mediated through A1 receptor antagonism rather than A2A receptor antagonism [8].

The adenosine receptor antagonism is the shared mechanism of action across the methylxanthine class and is the primary basis for the stimulant, wake-promoting, and anti-fatigue effects of paraxanthine at standard oral doses.

4.2 Selective PDE9 inhibition

Phosphodiesterases (PDEs) are intracellular enzymes that hydrolyze cyclic nucleotide second messengers (cAMP and cGMP), terminating their signaling actions. PDE9 is a cGMP-preferring phosphodiesterase expressed in the brain (hippocampus, cortex, cerebellum, basal ganglia), kidney, and other tissues. PDE9 hydrolyzes cGMP with high selectivity (approximately 100-fold preference for cGMP over cAMP) and regulates intracellular cGMP pools generated by both nitric oxide-stimulated soluble guanylyl cyclase and natriuretic peptide-stimulated particulate guanylyl cyclase [23].

Paraxanthine is a selective inhibitor of PDE9 activity, an action that is unique among the naturally occurring methylxanthines; caffeine, theophylline, and theobromine do not exhibit this selectivity [9, 10]. By inhibiting PDE9-mediated hydrolysis of cGMP, paraxanthine elevates intracellular cGMP levels in neurons and other target cells. The downstream consequences of elevated cGMP include activation of protein kinase G (PKG), modulation of ion channel conductance, potentiation of synaptic plasticity, and augmentation of glutamate and dopamine release. The PDE9 inhibitory mechanism is hypothesized to be the principal molecular basis for the procognitive effects of paraxanthine that exceed those predicted by adenosine receptor antagonism alone [10].

The PDE9 inhibitory activity places paraxanthine in a pharmacological class with dedicated PDE9 inhibitor drug candidates (BAY 73-6691, PF-04447943, BI 409306) that have been explored for cognitive enhancement in Alzheimer's disease and schizophrenia, providing a mechanistic bridge between the methylxanthine pharmacology literature and the broader cGMP-cognition research field [23].

4.3 Ryanodine receptor channel activation

Ryanodine receptors (RyR1, RyR2, RyR3) are intracellular calcium release channels located on the endoplasmic and sarcoplasmic reticulum membrane. In neurons, ryanodine receptor activation produces a moderate, sustained increase in free cy-

tosolic calcium that contributes to calcium-dependent signaling, synaptic plasticity, and cellular stress responses.

Bhatt et al. (2008) demonstrated that paraxanthine provides protection against MPTP-induced dopaminergic cell death in mouse striatal neurons, and that this neuroprotective effect is not mediated by adenosine receptor blockade or by elevation of intracellular cAMP, but is instead attributable to a moderate increase in free cytosolic calcium via activation of ryanodine receptor channels [11]. The ryanodine receptor mechanism was confirmed by blockade experiments with dantrolene (a ryanodine receptor antagonist), which abolished the neuroprotective effect.

This mechanism is unique to paraxanthine among the methylxanthines studied to date and provides a molecular basis for neuroprotective activity in dopaminergic neurodegeneration models relevant to Parkinson's disease research. The moderate calcium signal produced by ryanodine receptor activation (in contrast to the large, potentially excitotoxic calcium transients produced by some other agents) is considered to be within the neuroprotective range of calcium signaling.

4.4 Nitric oxide signaling potentiation

Paraxanthine, uniquely among the methylxanthines, potentiates nitric oxide (NO) neurotransmission [9]. Nitric oxide is a gaseous signaling molecule produced by neuronal nitric oxide synthase (nNOS) in the central nervous system and by endothelial nitric oxide synthase (eNOS) in the vasculature. In neurons, NO activates soluble guanylyl cyclase, increasing cGMP production, which in turn activates protein kinase G and modulates synaptic transmission and plasticity.

The potentiation of NO signaling by paraxanthine, in combination with the PDE9 inhibitory activity (which prevents cGMP degradation), produces a synergistic elevation of cGMP-mediated signaling in target neurons. This dual mechanism is hypothesized to increase glutamate and dopamine release in cortical and striatal circuits and to underlie the enhanced cognitive performance observed in behavioral studies [9, 10].

4.5 Composite pharmacology and selectivity

The composite pharmacology of paraxanthine at a 200 mg oral dose in humans produces approximate plasma concentrations in the low micromolar range at peak (approximately 5 to 15 micromolar depending on CYP1A2 phenotype and time since

administration). At these concentrations, adenosine A1 receptor antagonism is substantial (K_i 21 micromolar, plasma concentrations approaching or at K_i); A2A receptor antagonism is partial (K_i 32 micromolar); PDE9 inhibition is functionally relevant (based on pharmacological activity demonstrated at comparable concentrations in vitro); and ryanodine receptor activation occurs at concentrations consistent with the neuroprotective effects observed in cellular models [8, 9, 11].

The selectivity profile of paraxanthine relative to caffeine is therefore characterized by: (a) comparable adenosine receptor antagonism; (b) additional PDE9 inhibition absent from caffeine; (c) additional NO signaling potentiation absent from caffeine; (d) ryanodine receptor activation present in paraxanthine but not characterized in caffeine at equivalent concentrations; and (e) absence of the nonselective PDE inhibition that characterizes caffeine at higher concentrations. This composite profile provides the mechanistic basis for the observation that paraxanthine produces cognitive enhancement and neuroprotection that exceeds what adenosine receptor antagonism alone would predict.

5. Pharmacokinetics and Routes of Administration

5.1 Endogenous formation from caffeine

Paraxanthine is the principal first-step metabolite of caffeine in humans. After oral caffeine ingestion, hepatic CYP1A2 catalyzes the N3-demethylation of caffeine (1,3,7-trimethylxanthine) to paraxanthine (1,7-dimethylxanthine), accounting for approximately 80 to 84 percent of total caffeine biotransformation. Minor parallel pathways produce theophylline (N7-demethylation, approximately 4 to 5 percent) and theobromine (N1-demethylation, approximately 11 percent) [1, 7, 25].

The paraxanthine-to-caffeine plasma concentration ratio is the standard metabolic phenotyping probe for CYP1A2 activity and has been validated in both plasma and saliva matrices [19, 20]. The ratio increases with time after caffeine administration and reaches its maximum at approximately 4 to 8 hours post-dose, reflecting the formation kinetics of paraxanthine and the elimination kinetics of the parent caffeine. Paraxanthine plasma concentrations exceed those of caffeine approximately 8 to 10 hours after a single caffeine dose [7].

5.2 Absorption of exogenous paraxanthine

Exogenous paraxanthine administered orally is rapidly absorbed from the gastrointestinal tract. Time to peak plasma concentration (T_{max}) is approximately 1 to 2 hours after oral administration of 100 to 300 mg doses. Absorption is essentially complete, consistent with the physicochemical properties of the compound (low molecular weight, moderate lipophilicity, xanthine ring system). Food effects on absorption have not been extensively characterized, but the similarity in physicochemical properties to caffeine (which shows minimal food effect on overall exposure) suggests a modest food effect on rate but not extent of absorption [6, 17].

5.3 Distribution

Volume of distribution data for exogenous paraxanthine in humans have not been published in dedicated pharmacokinetic studies as of the monograph revision date. By inference from the caffeine pharmacokinetic literature and from the physicochemical similarity of the dimethylxanthine isomers, the volume of distribution is expected to be moderate (approximately 0.6 to 0.8 L/kg), with distribution into total body water. Plasma protein binding for paraxanthine is approximately 15 to 25 percent, lower than caffeine (approximately 36 percent), consistent with the lower molecular weight and the absence of the N3-methyl group [1].

The compound crosses the blood-brain barrier, as evidenced by its central nervous system pharmacological effects (stimulant, procognitive, neuroprotective) in both endogenous and exogenous administration contexts. Central nervous system penetration is expected to be comparable to caffeine based on physicochemical similarity.

5.4 Metabolism

Paraxanthine is further metabolized in the liver through several pathways: N-demethylation to 1-methylxanthine (by CYP1A2 and CYP2A6), N-demethylation to 7-methylxanthine, C8-oxidation to 1,7-dimethyluric acid (by xanthine oxidase), and acetylation to 5-acetylamino-6-formylamino-3-methyluracil (AFMU) by N-acetyltransferase 2 (NAT2) [1, 25]. The AFMU metabolite is notable because the AFMU-to-1-methylxanthine urinary ratio is used as a phenotyping probe for NAT2 acetylator status (fast versus slow acetylators), providing a second pharmacogenomic application of paraxanthine metabolism beyond the CYP1A2 phenotyping application.

5.5 Elimination

The plasma elimination half-life of paraxanthine is approximately 3.1 hours in healthy adults, which is shorter than caffeine (approximately 4.1 hours), theophylline (approximately 6.2 hours), and theobromine (approximately 7.2 hours) [3, 8]. The shorter half-life contributes to a more rapid offset of stimulant effects and a reduced potential for sleep disruption when consumed in the afternoon or evening relative to caffeine at equivalent doses.

Elimination is predominantly metabolic (hepatic biotransformation as described above) with excretion of metabolites in urine. Less than 5 percent of an administered dose is excreted unchanged in urine.

5.6 Special populations

CYP1A2 polymorphism and inducibility: CYP1A2 activity varies substantially across individuals (approximately 40-fold range in population studies) and is influenced by genetic polymorphism, smoking status (polycyclic aromatic hydrocarbons in cigarette smoke are potent CYP1A2 inducers), dietary factors (cruciferous vegetables induce CYP1A2; grapefruit juice inhibits), and concurrent medications (fluvoxamine is a potent CYP1A2 inhibitor) [19, 20]. When paraxanthine is administered as an exogenous supplement, these sources of variability affect the further metabolism and elimination of the compound but not its formation. The inter-individual variability in response to exogenous paraxanthine is therefore expected to be narrower than the variability in response to caffeine (where CYP1A2 determines both the formation of the active metabolite and the elimination of the parent compound).

Pediatric and geriatric populations: Dedicated pharmacokinetic studies of exogenous paraxanthine in pediatric and geriatric populations have not been conducted. The compound is marketed as a dietary ingredient for adult use.

6. Preclinical Pharmacology

6.1 Psychostimulant and locomotor effects

Ferré et al. (2013) conducted a comprehensive pharmacological comparison of paraxanthine and caffeine in rodent models [8]. Paraxanthine produced dose-dependent locomotor activation in rats with a potency modestly exceeding that of caffeine on a milligram-per-kilogram basis. The locomotor activation was primarily mediated through adenosine A1 receptor antagonism, as demonstrated by selective antagonist studies. At higher doses, paraxanthine produced less anxiogenic behavior than caffeine in the elevated plus-maze, consistent with a more favorable stimulant-to-anxiety ratio.

6.2 Cognitive enhancement in animal models

Alshabi et al. (2024) conducted a direct comparison of paraxanthine and caffeine effects on memory and neuroplasticity in young and aged rats [15]. In the Morris water maze, paraxanthine-treated groups showed significantly improved escape latency (indicative of spatial learning and memory) in both age cohorts. Hippocampal neurochemical analysis revealed that high-dose paraxanthine elevated BDNF levels to a greater extent than caffeine in both young and aged animals. Acetylcholine and dopamine levels were also elevated in paraxanthine-treated groups. Glutathione, a marker of antioxidant status, was significantly elevated in animals receiving high-dose paraxanthine, suggesting concurrent neuroprotective and antioxidant effects [15].

6.3 Neuroprotection against dopaminergic cell death

The Bhatt et al. (2008) study demonstrated that paraxanthine attenuated MPTP-induced dopamine depletion in mouse striatum [11]. The neuroprotective mechanism was independent of adenosine receptor blockade (as confirmed by experiments with selective adenosine receptor agonists and antagonists) and independent of cAMP elevation. Instead, the protection was mediated by activation of ryanodine receptor calcium release channels, producing a moderate increase in cytosolic calcium that triggered protective signaling cascades. Dantrolene, a ryanodine receptor

antagonist, abolished the neuroprotective effect. This finding is significant for Parkinson's disease research, as it identifies a molecular mechanism by which a caffeine metabolite with established epidemiological association with reduced Parkinson's risk could exert protective effects on the vulnerable dopaminergic neurons of the substantia nigra.

6.4 Ergogenic effects in rodents

Yoo et al. (2022) reported that paraxanthine supplementation in mice significantly increased forelimb grip strength by 17 percent, treadmill exercise performance by 39 percent, and muscle mass by 14 to 41 percent (depending on muscle group) relative to control [16]. The proposed mechanisms included increased plasma free fatty acid availability as a fuel source, reduction of plasma potassium concentrations (which may attenuate skeletal muscle fatigue onset), and increased calcium release in skeletal muscle involved in muscle contraction (consistent with the ryanodine receptor activation mechanism).

6.5 Lipolytic and metabolic effects

Paraxanthine has been demonstrated to enhance lipolysis and fatty acid mobilization in both animal and human studies. The compound increases plasma free fatty acid concentrations, stimulates fat oxidation, and enhances energy expenditure. The lipolytic activity is consistent with the adenosine A1 receptor antagonism in adipose tissue (adenosine acts as an antilipolytic signal through A1 receptors on adipocytes; antagonism releases this inhibition) and with the phosphodiesterase inhibition (which elevates cAMP in adipocytes, activating hormone-sensitive lipase) [17].

7. Clinical Evidence Base

7.1 Cognitive enhancement

Dose-response trial (Yoo et al., 2021): A double-blind, placebo-controlled, crossover trial examined the acute effects of paraxanthine at 50, 100, and 200 mg on cognitive function in healthy adults [12]. Participants completed a battery of cognitive assessments including the Go/No-Go task, N-back working memory task, psychomotor vigilance test, and the Stroop test at baseline and at multiple time points post-ingestion. Paraxanthine at 100 and 200 mg produced significant improvements in sustained attention, reaction time, and working memory relative to placebo. The 200 mg dose produced the largest effects on executive function and attentional stability. No clinically significant adverse events were reported at any dose.

Cognition and short-term memory trial (Xing et al., 2021): A double-blind, placebo-controlled, crossover trial of acute paraxanthine ingestion (200 mg, infinity) demonstrated improvements in cognition, short-term memory, and sustained attention in healthy adults [13]. The study reported significant effects on reaction time accuracy and attentional maintenance over the testing period, with effects persisting for several hours post-ingestion. Acute and 7-day daily paraxanthine ingestion was not associated with clinically significant side effects.

Post-exercise cognitive performance (Wells et al., 2024): A study examining cognitive function after a 10-kilometer run found that paraxanthine provided greater cognitive maintenance than caffeine in trained runners [14]. Subjects receiving caffeine committed 31 percent more errors on cognitive testing at the conclusion of the run, whereas subjects receiving paraxanthine improved correct responses by approximately 6.8 percent. The finding suggests that paraxanthine may provide superior cognitive resilience under conditions of physical fatigue relative to caffeine, potentially attributable to the additional PDE9 inhibition and NO signaling mechanisms that are not shared by caffeine.

7.2 Energy expenditure and metabolic effects

Dose-response metabolic study (2024): A study examining the effects of paraxanthine at 100, 200, and 300 mg on energy expenditure, appetite, and lipolysis in healthy adults reported that 200 mg paraxanthine significantly increased resting energy expenditure relative to placebo [17]. Hunger ratings increased significantly in the placebo group at multiple time points (30, 60, 90, and 180 minutes) but did not increase in the 200 mg paraxanthine group, suggesting an appetite-suppressive effect. Rates of fat oxidation tended to increase at 90 and 120 minutes with 200 mg paraxanthine, and free fatty acid concentrations were significantly elevated at 300 mg, confirming dose-dependent lipolytic activity. Blood pressure did not change in response to any paraxanthine dose, a notable safety advantage relative to caffeine at equivalent doses.

7.3 Exercise performance

Direct clinical evidence for ergogenic effects of exogenous paraxanthine in human exercise performance is emerging. The post-exercise cognitive data from Wells et al. (2024) provide indirect support [14]. Dedicated exercise performance trials examining paraxanthine effects on endurance, strength, and power output in trained athletes are in progress as registered clinical investigations (NCT06117280) [22].

7.4 Safety and tolerability in clinical studies

Across the published clinical studies, paraxanthine at doses of 50 to 300 mg administered acutely and for up to 7 days of daily administration has not been associated with clinically significant adverse events [6, 12, 13, 14, 17]. Specific findings include: no significant changes in systolic or diastolic blood pressure (in contrast to caffeine, which typically produces acute blood pressure elevations of 5 to 10 mmHg at equivalent doses); no significant changes in heart rate; no reported anxiety, jitteriness, or nervousness at rates exceeding placebo (in contrast to caffeine, which produces dose-dependent anxiety at the 200 to 400 mg range); and no reported sleep disruption in studies where paraxanthine was administered in the morning or early afternoon.

8. Sourcing and Quality Verification

The principal commercial source of synthetic paraxanthine for research and dietary supplement applications is the enfinity branded ingredient produced by Ingenious Ingredients (ING2), supplied at greater than 99 percent purity by HPLC. The compound is also available from multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, catalog number D5385; Cayman Chemical, catalog number 21068; Santa Cruz Biotechnology; TCI Chemicals; others) at greater than 98 percent purity by HPLC in milligram to gram quantities for research applications [4].

Quality verification recommendations: 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 (181.0720 for the protonated molecule $[M+H]^+$ or 180.0647 for the neutral monoisotopic mass)
- Comparison of retention time and spectral properties to an authentic reference standard (commercially available from Sigma-Aldrich and other suppliers)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis if the synthesis route is not disclosed by the supplier
- Verification that the material is the 1,7-dimethylxanthine isomer (not the 1,3-isomer theophylline or the 3,7-isomer theobromine) by NMR or by chromatographic comparison to all three dimethylxanthine isomers on a validated method

Isomeric purity consideration: Because paraxanthine, theophylline, and theobromine are positional isomers with identical molecular formulas and molecular weights, mass spectrometry alone is insufficient to confirm isomeric identity. Chromatographic or spectroscopic methods (NMR chemical shifts, HPLC retention time against all three isomers) are necessary to confirm that the supplied material is the correct isomer.

Pricing: Research-grade paraxanthine from Sigma-Aldrich is priced at approximately \$30 to \$50 per gram as of the monograph revision date. Bulk dietary-ingredient-grade material from Ingenious Ingredients is available at substantially lower per-gram cost for commercial applications.

9. Reconstitution and Handling

Paraxanthine is supplied as a white to off-white crystalline powder. The compound is sparingly soluble in water at room temperature (approximately 1 mg/mL) and is freely soluble in dimethyl sulfoxide (DMSO) and in warm water.

Stock solution preparation for in vitro research: Stock solutions are typically prepared at 10 to 100 mM in DMSO (18 mg/mL for a 100 mM stock in DMSO), aliquoted, and stored at minus 20 degrees Celsius. Working dilutions are prepared in the assay buffer or cell culture medium immediately before use. The final DMSO concentration in the assay should not exceed 0.1 to 0.5 percent (volume/volume) to avoid solvent effects on cellular systems. Aqueous stock solutions at lower concentrations (1 mM; 0.18 mg/mL) can be prepared in warm water or in phosphate-buffered saline with gentle heating.

Storage: The solid compound is stable at room temperature under normal ambient conditions. Long-term storage at 2 to 8 degrees Celsius in a desiccated, light-protected container is recommended for research-grade material. DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months. Aqueous solutions should be prepared fresh or used within 7 days of preparation and stored at 2 to 8 degrees Celsius.

Handling precautions: Standard laboratory precautions for handling fine crystalline powders (avoid inhalation, skin contact, eye contact). The compound is a central nervous system stimulant; accidental ingestion of research quantities should be treated as equivalent to caffeine exposure at the same dose.

Oral research formulations: For human dietary supplement and clinical research applications, paraxanthine is typically formulated in gelatin or vegetarian capsules at 50 to 200 mg per capsule, or as a powder blend in stick-pack or sachet format. The compound does not require special excipients for oral bioavailability but may benefit from a small amount of cellulose or silica as a flow agent for encapsulation.

10. Stack Interactions and Combinations

Paraxanthine interacts with several drug and supplement classes through its adenosine receptor antagonism, PDE9 inhibition, and metabolic pathways. Investigators and consumers using paraxanthine, especially in combination with other compounds, should consider the following:

Caffeine and other methylxanthines: Concurrent caffeine and exogenous paraxanthine produce additive adenosine receptor antagonism and potentially synergistic stimulant effects, as paraxanthine is already the principal active metabolite of caffeine. The combination increases total methylxanthine exposure and may exceed the threshold for anxiety, tachycardia, or sleep disruption that would not be reached by either compound alone. Individuals consuming exogenous paraxanthine should account for dietary caffeine intake from coffee, tea, and other sources.

CYP1A2 inhibitors: Fluvoxamine (the most potent clinical CYP1A2 inhibitor), ciprofloxacin, cimetidine, and oral contraceptive steroids reduce CYP1A2 activity and therefore slow the further metabolism of paraxanthine. Concurrent use may prolong paraxanthine exposure and half-life. The effect is smaller than with caffeine (where CYP1A2 inhibition affects both parent and metabolite kinetics) but is still pharmacologically relevant.

CYP1A2 inducers: Cigarette smoking, charcoal-grilled meat consumption, cruciferous vegetable intake, omeprazole, and rifampin induce CYP1A2 activity and accelerate paraxanthine metabolism. Smokers may require higher doses of paraxanthine to achieve equivalent pharmacological effects, consistent with the well-established higher caffeine requirements of smokers.

L-theanine: The combination of paraxanthine with L-theanine is under active clinical investigation (NCT07189442) for cognitive enhancement [21]. L-theanine (an amino acid found in tea) produces anxiolytic and attention-modulating effects through glutamate receptor modulation and GABA enhancement. The combination is hypothesized to preserve the procognitive effects of paraxanthine while attenuat-

ing any residual stimulant-associated anxiety. This combination mirrors the widely studied caffeine plus L-theanine stack but with the theoretical advantage of paraxanthine's lower anxiogenic profile.

PDE5 inhibitors (sildenafil, tadalafil): Paraxanthine's PDE9 inhibition elevates cGMP pools that are partially overlapping with those regulated by PDE5. Concurrent PDE5 inhibition could produce additive cGMP elevation, with potential consequences for blood pressure (hypotension), smooth muscle relaxation, and platelet function. The clinical significance of this interaction has not been studied but warrants consideration.

Adenosine (pharmacological): Paraxanthine antagonizes exogenous adenosine administered for supraventricular tachycardia or pharmacological stress testing. As with caffeine, patients receiving paraxanthine may require higher adenosine doses for clinical effect, and paraxanthine ingestion should be disclosed before adenosine-dependent cardiac procedures.

Sympathomimetic agents and stimulants: Concurrent use with ephedrine, synephrine, amphetamine, or other sympathomimetic stimulants produces additive cardiovascular stimulation (heart rate, blood pressure) and additive central nervous system excitation. The combination increases the risk of anxiety, insomnia, tachycardia, and hypertension.

Lithium: Methylxanthines, including paraxanthine, increase renal lithium clearance through adenosine receptor-mediated effects on renal tubular lithium reabsorption. Concurrent paraxanthine use in patients on lithium therapy may reduce lithium levels and compromise therapeutic control. Lithium levels should be monitored in patients who initiate or discontinue regular paraxanthine supplementation.

11. Adverse Events and Safety

11.1 Preclinical toxicology

Acute toxicity: The acute oral LD50 of paraxanthine in rats is 829.20 mg/kg body weight [6]. For comparison, the acute oral LD50 of caffeine in rats is approximately 192 to 381 mg/kg (depending on formulation and strain), indicating that paraxanthine is substantially less acutely toxic than the parent compound on a weight basis.

14-day repeat-dose toxicity: No mortality or treatment-related adverse effects were observed in rats receiving paraxanthine orally for 14 days at the doses studied [6].

90-day subchronic toxicity: In a 90-day repeat-dose oral toxicity study in rats, the NOAEL for paraxanthine was established at 185 mg/kg body weight per day [6, 18]. At this dose, there was no mortality and no treatment-related adverse effects in the paraxanthine group. In the comparator caffeine group at the same dose (185 mg/kg body weight per day), mortality was observed in two of the rats. Clinical signs observed in paraxanthine-treated animals at high doses included hyperactivity and hyperreflexia, which were completely reversed at the next-day observation and were not considered adverse events.

Genotoxicity and mutagenicity: In vitro bacterial reverse mutation assays (Ames test) and mammalian cell genotoxicity assays (micronucleus test, chromosomal aberration test) were negative for paraxanthine, indicating no evidence of genetic toxicity or mutagenicity [6]. This is a notable distinction from caffeine, which has produced positive clastogenic findings in some in vitro assays at high concentrations, and from theophylline, which is similarly clastogenic at high concentrations.

Teratogenicity: Paraxanthine has been reported to be less potent as a teratogen than caffeine or theophylline in animal models, consistent with the overall pattern of lower toxicity across the safety endpoints [18].

11.2 Clinical adverse events

In published human clinical studies of exogenous paraxanthine at doses of 50 to 300 mg administered acutely and for up to 7 days of daily administration, the following safety findings have been reported:

- No clinically significant adverse events at any studied dose [6, 12, 13, 14, 17]
- No significant changes in systolic or diastolic blood pressure (in contrast to caffeine, which produces acute elevations of approximately 5 to 10 mmHg)
- No significant changes in resting heart rate
- No reported anxiety, jitteriness, or nervousness at rates exceeding placebo
- No reported gastrointestinal adverse events (nausea, abdominal discomfort) at rates exceeding placebo
- No reported sleep disruption in studies where paraxanthine was administered in the morning or early afternoon
- No clinically significant changes in standard laboratory safety panels (hematology, blood chemistry, liver function tests, renal function tests)

11.3 Comparison to caffeine safety profile

The safety advantages of paraxanthine relative to caffeine are quantitative rather than qualitative: the compound shares the general methylxanthine mechanism of action but produces fewer adverse effects at equivalent stimulant doses. The principal distinguishing safety features are:

- Higher NOAEL in 90-day toxicity studies (185 versus 150 mg/kg body weight) [6, 18]
- Lower anxiogenic potential at equivalent stimulant doses (reduced anxiety-like behavior in rodent elevated plus-maze) [8]
- Absence of blood pressure elevation at doses up to 300 mg in human studies [17]
- Negative genotoxicity findings (versus mixed findings for caffeine in some assays)
- Shorter elimination half-life (3.1 versus 4.1 hours), reducing accumulation and sleep disruption risk
- Lower acute oral LD50 ratio relative to the effective dose, indicating a wider therapeutic index

11.4 Regulatory safety status

Paraxanthine (as the enfinity branded ingredient) has achieved self-affirmed GRAS status for use in food and beverages in the United States at levels up to 300 mg per serving [6]. This is 100 mg lower than the FDA's 400 mg daily recommendation for caffeine. The GRAS determination was based on the totality of the toxicology, pharmacokinetic, and clinical safety data. The compound is not approved as a pharmaceutical in any jurisdiction and does not carry a formal adverse-event reporting or postmarketing surveillance obligation.

11.5 Potential risk factors

Despite the favorable safety profile, the following risk factors should be considered:

- Individuals with caffeine sensitivity or caffeine-related anxiety disorders may also be sensitive to paraxanthine, as adenosine receptor antagonism is a shared mechanism
- Concurrent caffeine intake (from dietary sources) with exogenous paraxanthine supplementation increases total methylxanthine exposure
- Individuals taking CYP1A2 inhibitors (fluvoxamine, ciprofloxacin, oral contraceptives) may experience prolonged paraxanthine exposure
- Pregnancy and lactation safety data are limited; conservative avoidance is appropriate
- Pediatric safety data are absent; the compound is marketed for adult use only

12. Comparative Assessment

This section presents a structured comparative assessment of five stimulant and nootropic alternatives against paraxanthine, evaluated against five competency standards: novelty, effect size, promising potential (current research and commercial trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal alternatives that a researcher or consumer would consider in the same functional category as paraxanthine (methylxanthine stimulants, adenosine receptor-targeted compounds, and dietary nootropics).

12.1 Caffeine (1,3,7-trimethylxanthine)

Mechanism: Nonselective adenosine A1/A2A receptor antagonist, nonselective phosphodiesterase inhibitor. Caffeine is the parent compound from which paraxanthine is derived and is the world's most widely consumed psychoactive substance [1].

Novelty: None. Caffeine is the reference compound for the methylxanthine class and has been studied for over a century. It serves as the benchmark against which paraxanthine and other methylxanthine candidates are evaluated.

Effect size: Caffeine produces well-characterized improvements in alertness, attention, reaction time, and physical performance at doses of 100 to 400 mg. Cognitive effect sizes (Cohen's d) are typically 0.3 to 0.6 on attention and reaction time measures, comparable to paraxanthine at equivalent doses [12, 13, 14]. The ergogenic effects on endurance exercise are well established (approximately 2 to 4 percent improvement in time-trial performance).

Promising potential: High for continued use as a dietary ingredient and research tool. Low for novel therapeutic development. Caffeine's pharmacology is thoroughly characterized, and the compound is unlikely to produce novel findings beyond its established profile.

Side-effect profile: Caffeine produces dose-dependent anxiety, jitteriness, insomnia, blood pressure elevation, tachycardia, gastrointestinal disturbance, and habituation/withdrawal. The anxiogenic effects are pronounced at doses above 200

mg in sensitive individuals and are the principal tolerability limitation. Withdrawal headache and fatigue occur after chronic use cessation. The clastogenic potential in some in vitro assays is a preclinical safety consideration [6, 18].

Overall validation: Very high. Caffeine is the most extensively studied psychoactive compound in human pharmacology, with thousands of clinical trials and a multi-century safety record at dietary doses.

Comparison to paraxanthine: Paraxanthine offers the mechanistic advantages of PDE9 selectivity, NO signaling potentiation, and ryanodine receptor activation that are absent from caffeine, combined with a lower anxiogenic profile, a shorter half-life, absence of blood pressure effects, and a higher NOAEL. Caffeine offers the advantage of extensive validation, universal availability, very low cost, and regulatory acceptance in all global markets. The choice between the two depends on whether the additional mechanistic breadth and reduced side-effect burden of paraxanthine justify its higher cost and more limited safety database.

12.2 Theophylline (1,3-dimethylxanthine)

Mechanism: Nonselective phosphodiesterase inhibitor, adenosine A1/A2A receptor antagonist, histone deacetylase activator. Theophylline is primarily used clinically as a bronchodilator for asthma and chronic obstructive pulmonary disease [2].

Novelty: None for stimulant or cognitive applications. The compound is an established pharmaceutical with a narrow therapeutic index and is not positioned for cognitive enhancement or dietary use.

Effect size: Theophylline produces central nervous system stimulation at therapeutic bronchodilator doses (plasma concentrations of 10 to 20 micrograms/mL) but is not used for cognitive enhancement. The narrow therapeutic index limits dose escalation for stimulant purposes.

Promising potential: Low for cognitive or stimulant applications. The compound is in declining clinical use even for its registered bronchodilator indication, being superseded by inhaled corticosteroids and long-acting beta-agonists.

Side-effect profile: Theophylline has the least favorable safety profile of the common methylxanthines. Adverse events include nausea, vomiting, tachycardia, seizures (at supratherapeutic concentrations), and arrhythmias. The narrow thera-

peutic index (target plasma concentration 10 to 20 micrograms/mL, toxicity above 20 micrograms/mL) requires therapeutic drug monitoring. Theophylline is clastogenic in vitro and more potent as a teratogen than paraxanthine [3, 18].

Overall validation: High as a bronchodilator (decades of clinical use). Low as a stimulant or cognitive agent.

Comparison to paraxanthine: Paraxanthine is substantially safer than theophylline, has a wider therapeutic index, produces less gastrointestinal toxicity, is not clastogenic, and has the additional PDE9 selectivity and NO potentiation mechanisms that theophylline lacks. Theophylline has no advantages over paraxanthine for stimulant, cognitive, or dietary applications.

12.3 Dynamine (methylliberine, 2-methyl-2-(dimethylamino)carbonyl-1-methyluric acid)

Mechanism: Purine alkaloid structurally related to the methylxanthines, proposed to act through adenosine receptor antagonism and modulation of dopamine reuptake. The precise molecular pharmacology is less well characterized than that of the methylxanthines [26].

Novelty: Moderate. Dynamine is a relatively new entrant in the dietary supplement stimulant space, marketed as a rapid-onset, short-duration complement to caffeine and theacrine.

Effect size: Published data on Dynamine as a standalone ingredient are limited. The compound is typically studied in combination with caffeine and/or theacrine, making it difficult to isolate its independent contribution. Available data suggest modest acute stimulant effects with rapid onset and short duration.

Promising potential: Low to moderate. The compound occupies a niche position in the supplement market as a stacking ingredient rather than a standalone agent. The research base is thin relative to paraxanthine and caffeine.

Side-effect profile: Limited safety data. Available clinical data at supplement doses (100 to 200 mg) have not identified significant adverse events. Comprehensive toxicology has not been published to the extent of the paraxanthine or caffeine datasets.

Overall validation: Low. The compound has limited peer-reviewed research and no published comprehensive toxicology. It is commercially available but its pharmacology is not as well characterized as paraxanthine or caffeine.

Comparison to paraxanthine: Paraxanthine has substantially greater mechanistic characterization, a deeper safety database, more rigorous clinical evidence for cognitive effects, and a clearer regulatory pathway (GRAS status). Dynamine may offer complementary kinetics (faster onset, shorter duration) for stacking applications but does not have the standalone evidence base of paraxanthine.

12.4 Theacrine (1,3,7,9-tetramethyluric acid)

Mechanism: Purine alkaloid found in kucha tea (*Camellia assamica* var. kucha), proposed to act through adenosine receptor antagonism (both agonist and antagonist activities have been reported depending on dose and receptor subtype) and dopaminergic modulation [27].

Novelty: Moderate. Theacrine has received substantial research attention since approximately 2012 as a non-habituating alternative to caffeine, with the proposed advantage of sustained efficacy without tolerance development.

Effect size: Published clinical data suggest modest improvements in energy, focus, and motivation at doses of 200 to 300 mg, with effects broadly comparable to caffeine at equivalent doses. A key claimed advantage is the absence of habituation over 8 weeks of daily use, though this finding requires replication in larger cohorts [27].

Promising potential: Moderate. The compound has self-affirmed GRAS status (as the TeaCrine branded ingredient) and is incorporated into multiple consumer supplement products. The non-habituation claim, if confirmed in larger studies, would represent a meaningful advantage over caffeine and potentially over paraxanthine.

Side-effect profile: Available clinical data at supplement doses (200 to 400 mg) have not identified significant adverse events. The safety profile appears comparable to caffeine at equivalent doses. Comprehensive long-term toxicology is less extensive than for paraxanthine.

Overall validation: Moderate. The compound has a growing but still limited peer-reviewed research base, self-affirmed GRAS status, and commercial availability.

Comparison to paraxanthine: Paraxanthine has mechanistic advantages (PDE9 selectivity, NO potentiation, ryanodine receptor activation) that are not present in theacrine. Paraxanthine has demonstrated superior cognitive effects relative to caffeine in head-to-head studies; theacrine has not demonstrated superiority to caffeine on cognitive endpoints. Theacrine may offer the advantage of non-habituation if this finding is confirmed. Both compounds have self-affirmed GRAS status.

12.5 Alpha-GPC (L-alpha-glycerylphosphorylcholine)

Mechanism: Cholinergic precursor that increases acetylcholine synthesis and release in the brain following oral absorption and blood-brain barrier penetration. The mechanism is fundamentally different from the methylxanthine adenosine antagonist approach [28].

Novelty: Low. Cholinergic precursor supplementation for cognitive enhancement has been studied since the 1980s. Alpha-GPC is the most bioavailable oral choline source but the mechanism is well established.

Effect size: Published clinical data suggest modest improvements in memory and attention in elderly subjects and in patients with mild cognitive impairment at doses of 400 to 1200 mg daily. Effect sizes are small (Cohen's d approximately 0.2 to 0.4 on memory measures). The acute stimulant and attention effects are less pronounced than those of methylxanthines [28].

Promising potential: Moderate. The compound is widely available as a dietary supplement, is well tolerated, and has a long safety record. It does not produce stimulant effects comparable to paraxanthine and occupies a different functional niche (cholinergic support versus stimulant/nootropic).

Side-effect profile: The compound is well tolerated at standard doses. Reported adverse events are mild and include headache, heartburn, and insomnia at high doses. There are no significant safety concerns at dietary supplement doses.

Overall validation: Moderate. The compound has a substantial clinical evidence base for cholinergic cognitive support, primarily in elderly and cognitively impaired populations. Evidence in healthy young adults is more limited.

Comparison to paraxanthine: Alpha-GPC and paraxanthine have entirely different mechanisms of action and are complementary rather than competitive. Alpha-GPC provides cholinergic substrate support while paraxanthine provides adeno-

sine antagonism, PDE9 inhibition, and NO potentiation. Combination use is plausible and has been explored in supplement formulations. For acute cognitive enhancement and stimulant effects, paraxanthine has stronger clinical evidence; for long-term cholinergic support, Alpha-GPC has a more established evidence base.

12.6 Comparator summary

The five comparator compounds occupy distinct positions relative to paraxanthine. **Caffeine** is the reference standard, with unmatched validation and availability but a less favorable side-effect profile and mechanistic narrowness relative to paraxanthine. **Theophylline** is inferior to paraxanthine on every dimension relevant to stimulant and cognitive applications. **Dynamine** is a poorly characterized newer entrant without the evidence base to support standalone use. **Theacrine** is the most directly competitive alternative, with the potential advantage of non-habituation but without paraxanthine's mechanistic depth or demonstrated cognitive superiority to caffeine. **Alpha-GPC** operates through a complementary cholinergic mechanism and is a stacking candidate rather than an alternative.

Paraxanthine occupies a unique position in this comparator landscape: it is the only compound with demonstrated cognitive superiority to caffeine in controlled head-to-head studies, the only compound with selective PDE9 inhibition, the only compound with characterized ryanodine receptor neuroprotective activity, and the compound with the most favorable safety-to-efficacy ratio among the methylxanthine stimulants. Its principal limitation relative to caffeine is the smaller safety database and shorter commercial track record.

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the United States for dietary ingredient use at levels up to 300 mg per serving. Investigators should obtain analytical confirmation of identity, isomeric purity, and chemical purity on every research-grade lot.