Review Article **Open Access**

A natural nootropic for cognitive enhancement: A case study on the standardized mango leaf extract Zynamite®

Ana Beltrán-Arranz[1, †,*], David Fuentes-Ríos[1, 2,†], Rubén Pérez-Machín[1], Laura López-Ríos[1]

[1] Nektium Pharma S.L., C/Las Mimosas 8, Polígono Industrial Arinaga, 35118 Las Palmas, Spain; [2] Department of Organic Chemistry, Faculty of Sciences, University of Malaga, Campus de Teatinos s/n, 29071 Málaga, Spain

[*]**Corresponding author:** Ana Beltrán-Arranz, PhD, Research and Development Department, Nektium Pharma S.L., C/Las Mimosas 8, Polígono Industrial Arinaga, 35118 Las Palmas, Spain.

[†] These authors contributed equally to this work.

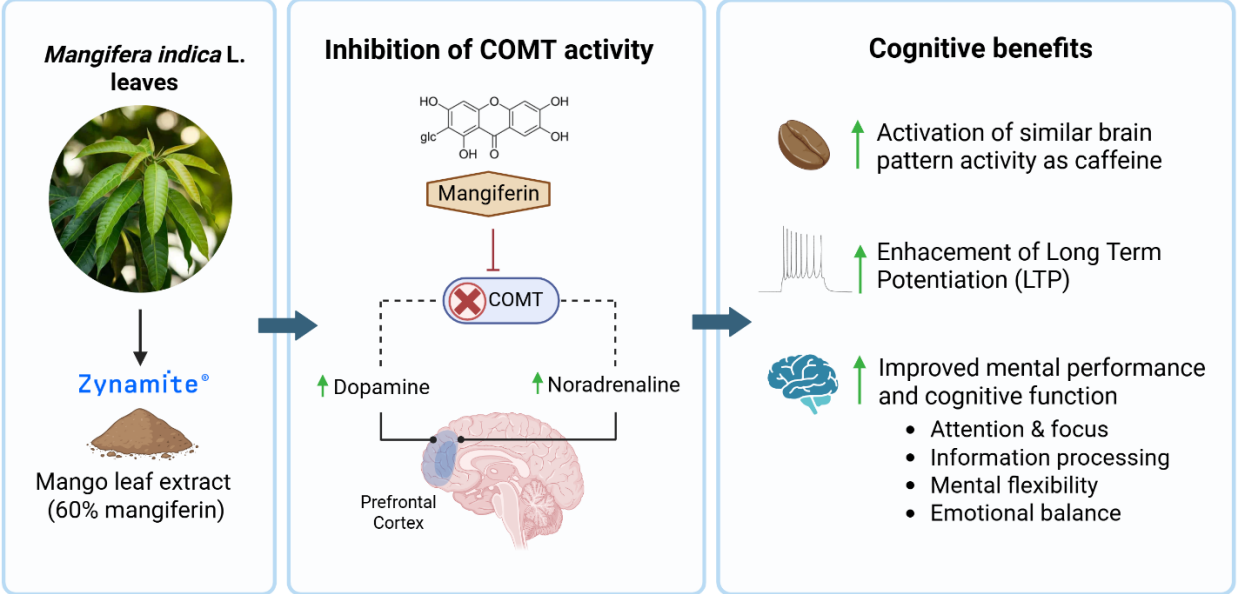
Submission Date: December 4th, 2025; **Acceptance Date:** January 29th, 2026; **Publication Date:** February 5th, 2026

Please cite this article as: Beltrán-Arranz A., Fuentes-Ríos D., Pérez-Machín R., López-Ríos L. A natural nootropic for cognitive enhancement: A case study on the standardized mango leaf extract Zynamite®. *Functional Foods in Health and Disease* 2026; 16(2): 118 – 131. DOI: https://doi.org/10.31989/ffhd.v16i2.1855

ABSTRACT

The demand for natural nootropics to enhance cognitive function has grown significantly. *Mangifera indica* L. (mango) leaves, with a long history of use in traditional medicine, have recently emerged as a promising candidate. Historically used as a tonic to combat fatigue and exhaustion, mango leaves are now the subject of rigorous scientific investigation. This review synthesizes the ethnobotanical background, phytochemical profile, and neuropharmacological activities of mango leaf extract and its principal bioactive compound, mangiferin. We delve into the mechanisms by which mangiferin impacts the central nervous system (CNS), including its antioxidant, anti-inflammatory, and neurotransmitter-modulating properties. A central component of this review is a detailed case study on Zynamite®, a standardized mango leaf extract. We examine preclinical and clinical evidence supporting its efficacy in enhancing cognitive domains such as reaction time, attention, and memory, particularly under conditions of stress and mental fatigue. To further optimize clinical outcomes, we detail the development of Zynamite® S, a version engineered to improve solubility and address pharmacokinetic hurdles. While previous literature has broadly discussed the diverse bioactivities of mango leaves, this article represents the first comprehensive review to specifically synthesize its effects on CNS and cognitive performance. By bridging the gap between traditional wisdom and modern science, this work provides a unique translational perspective on mango leaf extract as an evidence-based natural nootropic.

Keywords: Mango Leaf Extract, Cognitive Enhancement, Solubility, Zynamite®



Graphical Abstract: From Molecular Mechanism to Clinical Efficacy: The Neuromodulatory Profile of the standardized *Mangifera indica* leaf extract Zynamite®.

INTRODUCTION

Nootropics, often referred to as "smart drugs" or cognitive enhancers, are substances that can improve mental functions such as memory, creativity, motivation, and attention [1]. While pharmaceutical nootropics are prescribed for various conditions, there is a growing interest in natural, plant-derived compounds that can support cognitive health and performance without the side effects associated with synthetic stimulants [2]. This trend is driven by a growing consumer base, including students and professionals, seeking to manage the cognitive demands of modern life, which often involve high levels of stress that can impair attention and executive functions [3].

Within the vast repository of traditional medicine, the leaves of the mango tree, *Mangifera indica* L., have a long and storied history of use [4]. Cultivated for over 4,000 years, the mango tree holds a sacred place in many cultures, particularly in India, where its leaves are used as traditional remedies [5]. Ethnobotanical records document the use of mango leaf infusions as a general tonic and a specific remedy for fatigue and exhaustion. This historical precedent has provided a compelling rationale for modern scientific inquiry into the neurocognitive effects of mango leaves.

The scientific discipline of ethnopharmacology, which investigates the pharmacological basis of traditional medicines, has been instrumental in validating these ancient uses. Research has transitioned from documenting folk remedies to identifying active phytochemicals and elucidating their mechanisms of action through preclinical and clinical studies [6]. This review will trace the journey of *Mangifera indica* leaves from a traditional tonic to a scientifically validated natural nootropic. We will explore its ethnobotanical roots, its rich phytochemical composition, and the specific bioactivities of its primary constituent, mangiferia, on the CNS. A significant part of this review is dedicated to a case study of Zynamite®, a standardized mango leaf extract, examining the body of evidence from preclinical and human trials that substantiates its role in cognitive enhancement.

Methodology: A systematic literature review was performed across PubMed, Scopus, Web of Science, and the Functional Foods in Health and Disease (FFHDJ.com) database to identify relevant studies on the ethnobotanical, phytochemical, and neuropharmacological profiles of *Mangifera indica* L. leaves. The search covered publications from 2005 through 2025, with a particular emphasis on recent advancements in the effects of mango leaf extract in cognitive health. Search strategies utilized keywords, including: "mango leaf extract," "*Mangifera indica*," "mangiferin," and "Zynamite," cross-referenced with terms such as "cognitive performance," "nootropic," "phytochemistry," and "bioavailability." The initial screening of publications was performed collaboratively by authors A.B.A. and D.F.R. The inclusion criteria covered *in vitro* mechanistic studies, *in vivo* animal models, and human clinical trials. Data extraction focused on several key parameters, such as mango leaves' traditional uses and phytochemical profiles, experimental details, CNS molecular targets, and functional outcomes related to cognitive performance.

The quality of the evidence was assessed qualitatively based on the methodological rigor of the studies, giving special attention to the sample size, robust analysis, and study design, prioritizing randomized, double-blind, placebo-controlled studies. The findings were synthesized narratively and categorized into thematic sections: ethnobotanical uses of mango leaves, chemical composition, mechanism of action, and the clinical efficacy of standardized formulations. Despite the depth of the literature, certain limitations were identified, including high methodological variability and a lack of long-term longitudinal studies in humans. These factors limited the feasibility of performing a formal meta-analysis and required a qualitative synthesis of cross-study data.

Ethnobotanical and Phytochemical Profile of Mango Leaves: Traditional Uses of Mango Leaves: The mango tree, *Mangifera indica* L., a member of the *Anacardiaceae* family, is a species of profound cultural, religious, and medicinal significance [7], particularly within the Indian subcontinent where it has been cultivated for approximately 4,000 years. This deep-rooted history forms the basis of a rich ethnobotanical legacy, where every part of the plant—from root to fruit—has been used to treat a vast spectrum of human ailments [8]. The leaves have been employed in folk medicine across tropical regions as health teas, vegetables, and remedies to treat a wide array of conditions [4].

The most prominent and widely documented traditional use of mango leaves is in the management of metabolic disorders, particularly diabetes mellitus and its associated hyperglycemia for balancing blood sugar levels [9]. Mango leaves are also traditionally employed as a hypotensive agent to manage high blood pressure and as a general tonic for the circulatory system [10]. Their role in promoting gastrointestinal health is also extensive, as they are used as a stomachic to aid digestion and treat gastrointestinal issues such as diarrhea, dysentery, and stomach ulcers [11]. In respiratory health, mango leaves are a common folk remedy for ailments such as asthma, bronchitis, coughs, and other throat affections [12]. Other traditional uses include treating gall and kidney stones and urinary infections. Additionally, mango leaves are used topically to treat burns and heal wounds due to their antimicrobial and antiseptic properties [13].

While the most widely documented applications are related to metabolic disorders, gastrointestinal issues, and respiratory ailments, a deeper examination of ethnobotanical records revealed a consistent pattern of use for conditions related to the central nervous system. Across various cultures, mango leaves have been used as

a substitute for tea to combat exhaustion and fatigue [14]. This specific application suggests a perceived psychostimulant or energy-boosting effect. Furthermore, traditional practices describe using mango leaves to alleviate "restlessness" or anxiety and promote a sense of calm and relaxation. These traditional concepts of a fatigue-reducing and invigorating agent provide direct ethnobotanical precursors for the modern scientific investigation of mango leaf extract as a nootropic substance.

Phytochemical Composition of Mango Leaves: The broad spectrum of ethnobotanical uses of mango leaves reflects their complex phytochemical profile. The leaves are a rich source of diverse bioactive compounds, including terpenoids, flavonoids, phenolic acids, xanthones, and tannins [15,16] (Table 1). Among the flavonoids, kaempferol, quercetin and its glycosides (e.g., quercetin-3-O-glucoside) are present in notable concentrations, ranging between 1.00 and 11.00 mg/g of dry weight (DW). Phenolic acids, including gallic acid (0.5 – 3.0 mg/g DW), 5-Caffeoylquinic acid (0.7 - 1.6 mg/g DW), 3-chlorogenic acid (1.0- 8.0 mg/g DW), and 4-hydroxybenzoid acid (11.0 – 22.0 mg/g DW) are also present in significant concentrations [17]. Additionally, the leaves contain a variety of triterpenoids, including lupeol and cycloartane derivatives, along with phytosterols like β-sitosterol. Volatile organic compounds, primarily monoterpenes and sesquiterpenes, are responsible for the characteristic aroma and essential oil of the leaves; notable examples include cyperene, α-humulene, α-gurjunene, β-selinene, and β-caryophyllene [16].

Within this complex chemical matrix, the C-glycosyl xanthones have emerged as the principal family of bioactive constituents (Table 1). This group includes important compounds such as neomangiferin, homomangiferin, and most notably, mangiferin. Mangiferin is a specific C-glucosyl xanthone (1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside), a type of polyphenol found in high concentrations in mango leaves. Its unique chemical structure, featuring a stable C-glucosyl linkage and multiple hydroxyl groups, endows it with a remarkable spectrum of biological activities [18]. A vast body of scientific literature now attributes most of the observed pharmacological effects of mango leaf extract—including its antioxidant, anti-inflammatory, anti-diabetic, and neuroprotective properties—to the presence of mangiferin [15]. Although this xanthone is also present inmango bark and fruit peels, the especially high concentration in mango leaves positions them as a primary source of this valuable therapeutic agent, forming the cornerstone of modern research into their medicinal potential. The concentration of mangiferin can vary significantly depending on factors such as the mango cultivar, geographical location, leaf age (young vs. old), and the extraction method employed. The highest concentration of mangiferin occurs in leaves, ranging from 11.0 to 35.6 mg/g DW in old leaves and 36.9 to 67.2 mg/g DW in young leaves [19].

Table 1. Phytochemical Profile and Bioactive Compounds.

Chemical Class	Specific Compound	Concentration (mg/g DW*)	References
Flavonoids	Kaempferol, quercetin, and glycosides (e.g., quercetin-3-O-glucoside)	1.00 – 11.00	Wu et al., 2020
Phenolic Acids	Gallic acid	0.5 – 3.0	Wu et al., 2020
	5-Caffeoylquinic acid	0.7 – 1.6	
	3-Chlorogenic acid	1.0 – 8.0	
	4-Hydroxybenzoic acid	11.0 – 22.0	

Chemical Class	Specific Compound	Concentration (mg/g DW*)	References
C-glycosyl Xanthones	**Mangiferin** (Old leaves)	11.0 – 35.6	Ge et al., 2011; Kaur et al., 2025
	Mangiferin (Young leaves)	36.9 – 67.2	
	Neomangiferin, Homomangiferin, Northyriol	*Identifies (No mass quantification)*	
Triterpenoids & Phytosterols	Lupeol, cycloartane derivatives, β-sitosterol	*Not specified*	Ali et al., 2020
Volatile Organic Compounds	Cyperene, α-humeleno, α-gurjunen, β-selinene, β-caryophyllene	*Aroma constituents*	Kaur et al., 2025

**DW = Dry weight. The data reflects a compilation of various studies on multiple cultivars.*

Mango leaves are considered a valuable nutritional resource, primarily due to their beneficial proximate composition, despite variations in the specific levels of macronutrients and micronutrients present in the leaves (Table 2). Mango leaves contain a high level of crude protein, typically ranging from 16.25% up to 18.59% [15]. The carbohydrate content is also substantial, showing variation from 30.60% to 60.61% [15,20]. Regarding fat content, the ether extract was found to be approximately 4.30%. On the other hand, the ash content, which serves as an indicator of essential minerals including potassium, calcium, magnesium, and iron, is recorded between 8.24% and 11.49%. The vitamin content, concretely vitamins A, B, C, and E, contribute to their overall nutritional and therapeutic value. Lastly, it is worth mentioning that the high crude fiber content, ranging from 10.60% to 13.99%, contributes to diabetes management by regulating post-prandial hyperglycemia and facilitating the excretion of water and toxins from the body [15,20].

Table 2. Proximate Composition and Nutritional Value.

Constituents	***Content (%)***	***Functional Value / Significance***	***References***
Carbohydrates	30.60 – 60.61	Significant source of energy.	Ali et al., 2020; Kaur et al., 2025
Crude Protein	16.25 – 18.59	High protein level for plant biomass.	Kaur et al., 2025
Crude Fiber	10.60 – 13.99	Aids in diabetes management (post-prandial hyperglycemia control) and toxin excretion.	Ali et al., 2020; Kaur et al., 2025
Ash (Minerals)	8.24 – 11.49	Indicator of essential minerals (K, Ca, Mg, Fe).	Ali et al., 2020
Ether Extract (Fat)	~ 4.30	Moderate lipid content.	Kaur et al., 2025
Vitamins	< 0.1% (Traces)	Vitamins A, B, C, and E (Therapeutic value).	Kaur et al., 2025

Bioactivities of Mangiferin on the Central Nervous System: The traditional use of mango leaves as a remedy for fatigue and a general tonic for well-being has been substantiated by extensive preclinical research. The diverse cognitive benefits of mango leaf extracts are primarily attributed to their principal bioactive compound, mangiferin. As a potent C-glucosylxanthone capable of crossing the blood-brain barrier [21], mangiferin exerts pleiotropic effects directly within the CNS through a sophisticated interplay of neurochemical modulation and cellular protection.

Modulation of Monoaminergic Systems via COMT Inhibition: While early research suggested mangiferin as a potential monoamine oxidase (MAO) inhibitor [22], a more recent *in-vitro* screening against around 100 CNS targets identified that mangiferin is a moderately potent

inhibitor of catechol-O-methyltransferase (COMT) [6]. This intracellular enzyme is critical for the metabolic inactivation of catecholamine neurotransmitters, including dopamine, norepinephrine, and epinephrine [23].

By inhibiting COMT, mangiferin enhances signaling of these neurotransmitters, particularly in the prefrontal cortex, a brain region where dopamine mediates executive functions like working memory, planning, and attention [24]. Enhanced dopaminergic and noradrenergic signaling can stabilize and protect information processing, a mechanism relevant for improving attention and executive function in healthy individuals and potentially in conditions like attention deficit hyperactivity disorder (ADHD) [25,26]. Additionally, the role of COMT inhibitors is well-established in the management of Parkinson's disease, where they prolong the action of L-dopa [27].

Mangiferin also influences the cholinergic system, which is vital for learning and memory. In particular, mangiferin has been shown to reverse memory deficits by directly inhibiting acetylcholinesterase (AChE), the enzyme that degrades acetylcholine, thereby increasing the availability of acetylcholine in the synapse [28].

This dual action—enhancing the dopaminergic and noradrenergic signaling and preserving the cholinergic signaling that consolidates it—provides a robust foundation for its cognitive-enhancing properties.

Broad-Spectrum Neuroprotection and Anti-inflammatory Pathways: The central nervous system is uniquely vulnerable to pathological insults due to its high metabolic rate, lipid-rich composition, and susceptibility to chronic neuroinflammation, a key driver in the progression of most neurodegenerative diseases. Underpinning its neuromodulatory effects, mangiferin provides robust antioxidant and anti-inflammatory activities [29].

Mangiferin has been shown to powerfully suppress neuroinflammatory cascades through multiple, synergistic pathways. It inhibits the activation of nuclear factor kappa B (NF-κB) [28], a master transcription factor for the inflammatory response. This action, in turn, blocks the downstream expression of numerous pro-inflammatory factors, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and cyclooxygenase-2 (COX-2) [30]. Furthermore, mangiferin directly modulates the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome [31]. In stress-induced models, it down-regulates the expression of NLRP3, the adaptor protein ASC, and caspase-1, which subsequently reduces the production of the highly inflammatory cytokines IL-1β and IL-18 [32]. Its anti-inflammatory action is also demonstrated by its ability to ameliorate cognitive deficits induced by lipopolysaccharide (LPS), a potent inflammatory agent, by decreasing IL-6 production within the hippocampus and improving lipid metabolism abnormalities [33]. In parallel to these actions, mangiferin acts as a potent antioxidant via activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway to protect neurons from oxidative damage and neurotoxicity [34].

Mitigation of Core Neuropathological Processes: These combined anti-inflammatory and antioxidant activities translate into a tangible protection against neurodegeneration. Mangiferin has demonstrated the capacity to preserve neuronal integrity under toxic conditions, specifically by preventing the depletion of Brain-Derived Neurotrophic Factor (BDNF) in the hippocampus in models of aluminum chloride (AlCl3)-induced neurotoxicity [35]. Broadening its therapeutic potential, mangiferin has also shown efficacy in models of focal cerebral ischemia, where it reduced brain edema and infarct size by inhibiting the NF-κB signaling pathway [30]. In the context of Alzheimer's disease pathology,

mangiferin has shown promise in preclinical models of tauopathy by reducing the hyperphosphorylation of tau protein in critical brain regions such as the cortex and hippocampus [36]. This molecular intervention is directly correlated with functional improvements in both spatial and episodic memory. More recently, mangiferin was found to inhibit amyloid aggregation and reduced amyloid-derived toxicity *in vitro*, emerging as a promising neuroprotective agent [37]. Furthermore, it has been shown to mitigate age-related cognitive decline in scopolamine-induced amnesia models, improving learning and memory by counteracting cholinergic deficits [37].

Extending its neuroprotective scope to Parkinson's disease models, mangiferin has been shown to attenuate dopaminergic neurodegeneration [38]. In the context of this pathology, mangiferin decreased α-synuclein accumulation in dopaminergic neurons through inhibition of AKR1C3 expression and activation of the Wnt/β-catenin signaling pathway [39]. An additional study showed that mangiferin's neuroprotective effects were translated into an improved locomotor function in 6-hydroxydopamine (6-OHDA) lesioned rats [40].

Zynamite®: A Case Study of a Standardized Mango Leaf Extract for Cognitive Enhancement: The robust preclinical data on mangiferin laid the groundwork for the development and clinical testing of standardized mango leaf extracts for human cognitive enhancement. Zynamite®, a mango leaf extract standardized to contain ≥ 60% mangiferin, has been the subject of a series of preclinical and clinical studies demonstrating its robust nootropic potential.

Preclinical Studies: Initial preclinical research aimed to elucidate the primary mechanisms underlying the neuromodulatory activity of Zynamite®. Using *in vivo* electroencephalogram (EEG) recordings in freely moving rats and *ex vivo* hippocampal slice preparations, it was shown that Zynamite® induced brain activation patterns similar to caffeine [21], specifically attenuating alpha2 and beta1 spectral frequencies—electrophysiological signatures associated with dopaminergic and glutamatergic neurotransmission, respectively. Notably, the co-administration of Zynamite® with low-dose caffeine elicited synergistic effects on spectral power attenuation and significantly enhanced Long-Term Potentiation (LTP) in the hippocampus [21]. These findings confirmed that the bioactive compounds in Zynamite® successfully crossed the blood-brain barrier to modulate neuronal excitability and suggested its therapeutic potential as a nootropic agent capable of enhancing cognitive function.

A subsequent study identified mangiferin as the primary CNS-active compound in Zynamite® and elucidated its distinct mechanism of action. Through broad *in vitro* screening against CNS targets, mangiferin was found to be a selective inhibitor of COMT, while showing no significant activity on adenosine receptors or phosphodiesterase 4 (PDE4) [6], thereby differentiating its primary mechanism of action from that of caffeine. In *ex vivo* hippocampal slice models, both isolated mangiferin and Zynamite® induced remarkably similar increases in population spike amplitude following theta burst stimulation [8], confirming their shared ability to enhance Long-Term Potentiation (LTP). This functional equivalence was further corroborated *in vivo* via quantitative electroencephalography (qEEG) in rats, in which oral administration of either compound elicited matching brain stimulatory signatures in the frontal cortex and the striatum, confirming that mangiferin is the principal bioactive responsible for the CNS-activating effects of the extract [6].

A comprehensive toxicological evaluation of Zynamite® established a No Observed Adverse Effect Level (NOAEL) of 2000 mg/kg bw/day in a 90-day repeated-dose rat study, with no evidence of target

organ toxicity [41]. In genotoxicity assessments, the Zynamite® showed no mutagenic potential in the bacterial reverse mutation (Ames) test. Furthermore, while initial *in vitro* chromosomal aberration test indicated potential clastogenicity, a subsequent *in vivo* mammalian micronucleus test demonstrated no genotoxic effects up to the limit dose of 2000 mg/kg bw, confirming the extract's safety profile *in vivo*.

Clinical Studies: Following the preclinical demonstration that Zynamite® modulates brain activity similarly to established nootropics, the imperative shifted to confirming that these findings translate into functional effects in humans. To address this, a series of rigorous double-blind, placebo-controlled, crossover clinical trials were undertaken.

Initial exploratory work found that a single 500 mg dose of Zynamite® significantly improved reaction time compared to placebo [6]. Furthermore, this study also evaluated different mood domains using the Profile of Mood States (POMS) psychometric questionnaire. Crucially, the results revealed that Zynamite® led to a significant reduction in fatigue, providing direct clinical validation for its ethnobotanical use. Importantly, Zynamite® was well-tolerated and did not produce any cardiovascular disturbances, as no variations in blood pressure or heart rate (pulse) were detected compared to placebo. The absence of cardiovascular disturbances appeared as a key differentiator, as other commonly used nootropics, such as caffeine, are frequently associated with undesirable side effects like increased heart rate, nervousness, and jitters. This favorable safety profile, combined with its demonstrated efficacy positioned Zynamite® as a promising natural nootropic.

These preliminary human data were powerfully corroborated by a subsequent larger trial, which demonstrated significant cognitive enhancement following administration of a single 300 mg dose of Zynamite® [42]. This pivotal study demonstrated that the extract significantly improved overall performance accuracy across a battery of cognitive tasks. Specifically, it enhanced performance on an 'Accuracy of Attention' and 'Episodic Memory' domain. These cognitive benefits were remarkably sustained across assessments at 30 minutes, 3 hours, and 5 hours post-ingestion.

Beyond its cognitive effects, Zynamite® in combination with other polyphenols has demonstrated to improve exercise performance by enhancing VO_2 peak and peak power output, attenuating exercise-induced muscle damage and exerting exercise-mimetic properties in the skeletal muscle [43-45].

The Evolution to Zynamite® S: Development and Clinical Validation: Despite the robust scientific background supporting Zynamite® as a potent natural nootropic, a significant challenge for mangiferin is its low oral bioavailability due to low aqueous solubility (0.111 mg/mL), which result in insufficient intestinal membrane permeability. Furthermore, mangiferin also shows a significant P-glycoprotein efflux, which contributes to its overall low bioavailability [46,47]. Consequently, higher doses are required to elicit cognitive function. To address this challenge, numerous strategies have been employed to improve the bioavailability of mangiferin, including molecular inclusion in natural polymer system [48], lipid emulsions containing surfactants [49], complexation into lipo- or phytosomes [50-53], glycosylation [54] and salt formation. It is important to highlight this last strategy, as several studies have demonstrated that mangiferin salt exhibits enhanced bioavailability in rat plasma compared to standard mangiferin [55,56]. Specifically, a highly soluble version of the *Mangifera* leaf extract, named Zynamite® S, was developed through a controlled ionization process to produce an extract containing mangiferin monosodium salt. This improved solubility has been shown to enhance mangiferin’s

pharmacokinetic properties, based on a comparative analysis in human plasma between the standard mangiferin leaf extract and its ionized form (Zynamite® S) [57]. The pharmacokinetic study revealed that mangiferin from Zynamite® S significantly improved the compound's bioavailability, resulting in a 2.44-fold increase in mangiferin absorption, measured by dose-normalized area under the concentration-time curve from 0-24h ($AUC_{0\text{-}24h}$) compared to the standard mango leaf extract. This difference was even more pronounced shortly after ingestion, with absorption being 3.19 times greater from Zynamite® S than from the standard formulation of one-hour post-administration.

This improved pharmacological profile directly translates to enhanced functional effects. A randomized, double-blind, placebo-controlled crossover study involving 119 university students over their exam period tested the effects of a single low dose of Zynamite® S [58]. The results demonstrated that participants receiving Zynamite® S experienced significant improvements in mood, with reduced scores for tension, depression, and confusion, suggesting enhanced mental clarity. The extract also improved cognitive function, specifically processing speed and cognitive flexibility. These benefits were sustained for at least five hours post-ingestion. These findings support Zynamite® S as a fast-acting natural nootropic capable of improving both cognitive function and emotional balance, making it particularly relevant for target groups like students and working professionals in high-stress environments.

Functional Food Practical Implications & Future Directions: The development of the standardized mango leaf extract Zynamite® aligns with the Functional Food Center's (FFC) 17-step model [59,60]. The research undertaken to date has determined relevant bioactive compounds by identifying mangiferin as the primary constituent and has established the appropriate dosage and time of consumption to ensure maximum efficacy without toxicity [61]. The work conducted has determined the specific pathway and mechanism of action by elucidating its role in COMT inhibition, while providing preclinical and clinical studies on efficacy and safety, with findings submitted to peer-reviewed, open-access journals to facilitate scientific transparency. By fulfilling these rigorous criteria, this research supports the official establishment and release of the functional food product to the market as a clinically validated intervention [62].

Strengthening its connection to the functional food framework [63], the next logical step involves expanding its versatility through optimized delivery systems. While traditional mango leaf extracts often face solubility challenges, the development of the new water-soluble formulation (Zynamite® S) allows for seamless integration into diverse food vehicles, including liquid formats (e.g., functional beverages), as well as chews, gummies, or sticks, without compromising taste or stability. Such practical applications are specifically designed to meet the needs of target populations—including university students, busy professionals, and overwhelmed parents—who require convenient, stimulant-free options for enhancing cognitive performance and mental energy. Future efforts should focus on developing personalized nutritional strategies and conducting clinical trials in these specific demographic subgroups to refine dosage and timing according to individual metabolic needs [64,65]. Such efforts will bridge the gap between scientific progress and daily dietary practices, ensuring that the standardized benefits of Zynamite® S are optimized for diverse real-world scenarios.

CONCLUSION

Mangifera indica leaves possess a rich ethnobotanical history as a traditional remedy for fatigue, restlessness,

and a wide array of other ailments. Modern scientific research has not only validated these traditional claims but has also uncovered the sophisticated neuropharmacological mechanisms that underpin them. The primary bioactive compound, mangiferin, exerts pleiotropic effects on the central nervous system through potent antioxidant, anti-inflammatory, and neurotransmitter-modulating activities, most notably as a COMT inhibitor. The novelty of this review lies in its targeted focus on the CNS, a domain previously overshadowed by research on the antidiabetic properties of mango leaves. Furthermore, this work offers practical implications for the functional food industry by detailing the technological evolution from standard extracts to high-solubility formulations.

The case study of Zynamite®, a standardized mango leaf extract, provides compelling clinical evidence for its efficacy as a natural nootropic. Human trials have demonstrated their ability to improve reaction time, attention, and memory while significantly reducing mental fatigue. The emerging evidence strongly supports the hypothesis that Zynamite® functions as a cognitive adaptogen, enhancing mental performance and resilience most effectively under conditions of high cognitive demand. The development of enhanced solubility formulations like Zynamite® S further promises greater efficacy at lower doses. By integrating ethnobotanical history with rigorous scientific validation, mango leaf extract has been firmly established as a promising, evidence-based natural agent for cognitive enhancement.

Abbreviations: 6-hydroxydopamine (6-OHDA), Acetylcholinesterase (AChE), Aluminum chloride (AlCl3), Area Under the Concentration-Time Curve from 0-24h ($AUC_{0\text{-}24h}$), Attention Deficit Hyperactivity Disorder (ADHD), Brain-Derived Neurotrophic Factor (BDNF), Central Nervous System (CNS), Catechol-O-methyltransferase (COMT), Cyclooxygenase-2 (COX-2), Interleukin-1 beta (IL-1β), Lipopolysaccharide (LPS), Long-Term Potentiation (LTP), Monoamide Oxidase (MAO), Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), Nuclear Factor kappa B (NF-κB), NOD-like Receptor Pyrin Domain-Containing Protein 3 (NLRP3), No Observed Adverse Effect Level (NOAEL), Profile of Mood States (POMS), Quantitative Electroencephalography (qEEG), Tumor Necrosis Factor-alpha (TNF-α).

Competing Interests: A.B.-A., D.F.-R., R.P-M., and L.L.-R. are employed by the company Nektium Pharma S.L., C/Las Mimosas 8, Polígono Industrial Arinaga, Las Palmas. The authors declare that their employment and commercial interests have not influenced the objective presentation of the general literature on mango leaves. The case study summarizes findings previously published and is presented to illustrate the practical application of the bioactive compounds described in the review.

Author's contribution: A.B.-A. – Conceptualization, Investigation (Literature Search), Validation, Visualization, Writing – original draft; D.F.-R. - Conceptualization, Investigation (Literature Search), Validation, Visualization, Writing – original draft; R.P.-M. - Validation, Writing – review and editing; L.L.-R. - Conceptualization, Supervision, Resources, Validation, Writing – review and editing. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Mirzaei M, Razi Z, Morowvat MH. The science of tomorrow: unearthing hidden discoveries of cognitive enhancers. *Brain Disord.* 2025; 20:100142. DOI: https://doi.org/10.1016/j.dscb.2025.100290
2. Malík M, Tlustoš P. Nootropic herbs, shrubs, and trees as potential cognitive enhancers. *Plants.* 2023;12(6):1364. DOI: https://doi.org/10.3390/plants12061364
3. Escano E, Sezer N, Pustjens AM. Investigating cognitive-enhancing supplement use among students at a Dutch life science university. *PLoS One.* 2025;20(10): e0332433.

DOI: https://doi.org/10.1371/journal.pone.0332433

4. Ediriweera MK, Tennekoon KH, Samarakoon SR. A review on ethnopharmacological applications, pharmacological activities, and bioactive compounds of *Mangifera indica* (mango). *Evid Based Complement Alternat Med.* 2017; 2017:6945343. DOI: https://doi.org/10.1155/2017/6949835
5. Swaminathan C, Sangeetha K, Nivethadevi P. Mango (*Mangifera indica* L.) leaves bring together the cultural values and scientific heritage of the Indians for centuries. *Ethnobot Res Appl.* 2023; 25:1:12. DOI: http://dx.doi.org/10.2139/ssrn.4417613
6. López-Ríos L, Wiebe J, Vega-Morales T, Gericke N. Central nervous system activities of extract *Mangifera indica* L. *J Ethnopharmacol.* 2020; =260:112996. DOI: https://doi.org/10.1016/j.jep.2020.112996
7. Sharma D, Gupta S, Kumar R, Singh P, Singh A, Khan H. An ethnopharmacological, phytochemical and pharmacological review on Mangifera indica (Mango). *Res. J. Pharmacol. Pharmacodyn.* 2024;16(1):30-4. DOI: https://doi.org/10.52711/2321-5836.2024.00006
8. Thomas J, Athulkrishna MU, Ashok A, Athul PB, Paul J. Mango leaves unveiled: a comprehensive review of their benefits and uses. *J. Pharmacogn. Phytochem.* 2025;14(1):130-4. DOI: https://doi.org/10.22271/phyto.2025.v14.i1b.15230
9. Zarasvand SA, Mullins AP, Arjmandi B, Haley-Zitlin V. Antidiabetic properties of mango in animal models and humans: A systematic review. *Nutr. Res.* 2023; 111:73-89. DOI: https://doi.org/10.1016/j.nutres.2023.01.003
10. Minniti G, Laurindo LF, Machado NM, Duarte LG, Guiguer EL, Araujo AC, et al. *Mangifera indica* L., by-products, and mangiferin on cardio-metabolic and other health conditions: a systematic review. *Life.* 2023;13(12):2270. DOI: https://doi.org/10.3390/life13122270
11. Stohs SJ, Swaroop A, Moriyama H, Bagchi M, Ahmad T, et al. A review on antioxidant, anti-inflammatory and gastroprotective abilities of mango (*Mangifera indica*) leaf extract and mangiferin. *J. Nutr. Health Sci.* 2018;5(3):303. DOI: https://doi.org/10.15744/2393-9060.5.303
12. Rajizadeh MA, Najafipour H, Bejeshk MA. An updated comprehensive review of plants and herbal compounds with antiasthmatic effect. *Evid. Based Complement. Alternat. Med.* 2024; 2024:5373117. DOI: https://doi.org/10.1155/2024/5373117
13. Mendonça D, Tan YZ, Lor YX, Ng YJ, Siyadatpadah A, Lim CL, Norouzi R, et al. A review on phytochemistry, ethnopharmacology, and antiparasitic potential of *Mangifera indica* L. *Pharmaceuticals.* 2025;18(10):1576. DOI: https://doi.org/10.3390/ph18101576
14. Rafiu BO, Omotayo AO, Lawal IO, Aremu AO. Ethnobotanical uses of plants in Nigeria: an analysis of current research trends and patterns. *J. Ethnobiol. Ethnomed.* 2025;21(1):57. DOI: https://doi.org/10.1186/s13002-025-00788-y
15. Kaur J, Kaushik D, Kumar M, Babagil GE, Amarowicz R, Proestos C, et al. Comprehensive analysis and characterization of *Mangifera indica* L. leaf powder. *Food Sci. Nutr.* 2025;13(6): e70083. DOI: https://doi.org/10.1002/fsn3.70083
16. Mehmood H, Mehmood J, Zulfiqar N. Exploring the phytochemistry and pharmacology of *Mangifera indica* L. (Mango) leaves: a review. *Int. J. Plant Based Pharm.* 2024;4(1):9-18. DOI: https://doi.org/10.29228/ijpbp.38
17. Wu L, Wu W, Cai Y, Li C, Wang L. HPLC fingerprinting-based multivariate analysis of phenolic compounds in mango leaves varieties: correlation to their antioxidant activity and in silico alpha-glucosidase inhibitory ability. *J. Pharm. Biomed. Anal.* 2020; 191:113616. DOI: https://doi.org/10.1016/j.jpba.2020.113616
18. Zivković J, Kumar KA, Rushendran R, Ilango K, Fahmy NM, El-Nashar HAS, et al. Pharmacological properties of mangiferin: bioavailability, mechanisms of action and clinical perspectives. *Naunyn Schmiedebergs Arch Pharmacol.* 2024;397(2): 763:781. DOI: https://doi.org/10.1007/s00210-023-02682-4
19. Ge DD, Zhang Y, Liu EW, Wang T, Hu LM. Chemical constituents of *Mangifera indica* leaves (I). *Chin Tradit Herb Drugs.* 2011;42(3): 428:431
20. Ali BA, Alfa AA, Tijani KB, Idris ET, Unoyiza US, Junaidu Y. Nutritional health benefits and bioactive compounds of *Mangifera indica* L (mango) leaves methanolic extracts. *Asian Plant Res J.* 2020;6(2): 41:51. DOI: https://doi.org/10.9734/aprj/2020/v6i230126
21. Dimpfel W, Wiebe J, Gericke N, Schombert L. Zynamite (*Mangifera indica* leaf extract) and caffeine act in a synergistic manner on electrophysiological parameters of rat central nervous system. *Food Nutr Sci.* 2018;9(5): 502:518. DOI: https://doi.org/10.4236/fns.2018.95039

22. Chaurasiya ND, Leon F, Muhammad I, Tekwani BL. Natural products inhibitors of monoamine oxidases—potential new drug leads for neuroprotection, neurological disorders, and neuroblastoma. *Molecules.* 2022;27(13):4297. DOI: https://doi.org/10.3390/molecules27134297
23. Bindra S, Datta A, Yasin HKA, Thomas RR, Verma S, Patel A, et al. Recent progress in synthetic and natural catechol-O-methyltransferase inhibitors for neurological disorders. *ACS Omega.* 2024;9(44):44005-18. DOI: https://doi.org/10.1021/acsomega.4c06190
24. Boyle N, Betts S, Lu H. Monoaminergic modulation of learning and cognitive function in the prefrontal cortex. *Brain Sci.* 2024;14(9):902. DOI: https://doi.org/10.3390/brainsci14090902
25. Madhusoodanan J. Untangling the connection between dopamine and ADHD. *Nature.* 2026. DOI: https://doi.org/10.1038/d41586-026-00094-x
26. MacDonald HJ, Kleppe R, Szigetvari PD, Haavik J. The dopamine hypothesis for ADHD: an evaluation of evidence accumulated from human studies and animal models. *Front. Psychiatry.* 2024; 15:1492126. DOI: https://doi.org/10.3389/fpsyt.2024.1492126
27. Jenner P, Nyholm D. COMT inhibition with entacapone for patients with Parkinson's disease and motor complications: the novelty of continuous infusion. *J. Neural Transm.* 2025. DOI: https://doi.org/10.1007/s00702-025-03006-x
28. Jung K, Lee B, Han SJ, Ryu JH, Kim DH. Mangiferin ameliorates scopolamine-induced learning deficits in mice. *Biol Pharm Bull.* 2009;32(2): 242:246. DOI: https://doi.org/10.1248/bpb.32.242
29. Mustafa AM, Bastawesy GA, Hatem S, Moussa RAG, Hal DM, Fawzy MH, et al. Polyphenolic protection: the role of mangiferin in mitigating neurodegeneration and neuroinflammation. *Inflammopharmacology.* 2025; 33:4535:4552. DOI: https://doi.org/10.1007/s10787-025-01854-3
30. Hao T, Chen C, Yang S, Zhang Y, Liang F. Mangiferin exerts neuroprotective effects against focal cerebral ischemia in mice by regulating NF-κB signaling pathway. *Metab. Brain Dis.* 2023;38(1):383–91. DOI: https://doi.org/10.1007/s11011-022-01066-6
31. Lei L, Chen CY, Wang YF, Guo ZY, Zhang Y. Mangiferin: A natural neuroprotective polyphenol with anti-inflammatory and anti-oxidant properties for depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2025; 139:111401. DOI: https://doi.org/10.1016/j.pnpbp.2025.111401
32. Cao C, Su M, Zhou F. Mangiferin inhibits hippocampal NLRP3 inflammasome and exerts antidepressant effects in a chronic mild stress mice model. *Behav. Pharmacol.* 2017;28(5):356–64. DOI: https://doi.org/10.1097/FBP.0000000000000305
33. Zhang H, Wang L, Wang X, Deng L, He B, Yi X, et al. Mangiferin alleviated poststroke cognitive impairment by modulating lipid metabolism in cerebral ischemia/reperfusion rats. *Eur J Pharmacol.* 2024; 977:176726. DOI: https://doi.org/10.1016/j.ejphar.2024.176724
34. Peng C, Zhang Y, Chai J, Zhang H. Mangiferin mitigates neurological deficits and ferroptosis via NRF2/ARE pathway activation in cerebral ischemia-reperfusion rats. *Front. Pharmacol.* 2025; 16:1577954. DOI: https://doi.org/10.3389/fphar.2025.1577954
35. Kasbe P, Jangra A, Lahkar M. Mangiferin ameliorates aluminium chloride-induced cognitive dysfunction via alleviation of hippocampal oxido-nitrosative stress, proinflammatory cytokines and acetylcholinesterase level. *J. Trace Elem. Med. Biol.* 2015; 31:107-12. DOI: https://doi.org/10.1016/j.jtemb.2015.04.002
36. Wang N, Sun Z, Chen F, Tian X, Li J, He X. Mangiferin alleviates formaldehyde-induced tau hyperphosphorylation and cognitive impairment in mice via the PI3K/AKT/GSK3β pathway: insights from network pharmacology and experimental validation. *FASEB J.* 2026;40(2): e71346. DOI: https://doi.org/10.1096/fj.202503159R
37. Florio D, Gallo E, Saviano A, Schettino A, Marigliano N, Leone I, et al. Mangiferin as a novel in vitro polyphenolic inhibitor of amyloid aggregation. *ACS Omega.* 2025;10(44): 52773:52782. DOI: https://doi.org/10.1021/acsomega.5c06703
38. Zhou H, Mao Z, Zhang X, Li R, Yin J, Xu Y. Neuroprotective effects of mangiferin on rotenone-induced Parkinson's disease mice model through the TLR4/MyD88/NF-κB signaling pathway. *ACS Chem. Neurosci.* 2023;14(8):1379-87. DOI: https://doi.org/10.1021/acschemneuro.2c00458
39. Huang W, Wang Y, Huang W. Mangiferin alleviates 6-OHDA-induced Parkinson's disease by inhibiting AKR1C3 to activate Wnt signaling pathway. *Neurosci. Lett.* 2024; 821:137608. DOI: https://doi.org/10.1016/j.neulet.2023.137608
40. Tiwari PC, Chaudhary MJ, Pal R, Nath R. Role of nitric oxide modulators in neuroprotective effects of mangiferin in 6-hydroxydopamine-induced Parkinson's disease in rats. *Ann. Neurosci.* 2024;31(3):186–203.

DOI: https://doi.org/10.1177/09727531231184698

41. Reddeman RA, Glávits R, Endres JR, Clewell AE, Hirka G, Vértesi A, et al. A toxicological evaluation of mango leaf extract (*Mangifera indica*) containing 60% mangiferin. *J. Toxicol.* 2019; 2019:4763015. DOI: https://doi.org/10.1155/2019/4763015
42. Wightman EL, Jackson PA, Forster J, Khan J, Wiebe JC, Gericke N, et al. Acute effects of a polyphenol-rich leaf extract of *Mangifera indica* L. (Zynamite) on cognitive function in healthy adults: a double-blind, placebo-controlled crossover study. *Nutrients.* 2020;12(8):2194. DOI: https://doi.org/10.3390/nu12082194
43. Bourdas DI, Travlos AK, Souglis A, Stavropoulou G, Zacharakis E, Gofas DC, et al. Effects of a singular dose of mangiferin–quercetin supplementation on basketball performance: a double-blind crossover study of high-level male players. *Nutrients.* 2024;16(1):153. DOI: https://doi.org/10.3390/nu16010170
44. Martinez-Canton M, Galvan-Alvarez V, Garcia-Gonzalez E, Gallego-Selles A, Gelabert-Rebato M, Garcia-Perez G, et al. A mango leaf extract (Zynamite) combined with quercetin has exercise-mimetic properties in human skeletal muscle. *Nutrients.* 2023;15(13):3054. DOI: https://doi.org/10.3390/nu15132848
45. Martinez-Canton M, Galvan-Alvarez V, Martin-Rincon M, Calbet JAL, Gallego-Selles A. Unlocking peak performance: the role of Nrf2 in enhancing exercise outcomes and training adaptation in humans. *Free Radic Biol Med.*2024; 224:168:181. DOI: https://doi.org/10.1016/j.freeradbiomed.2024.08.011
46. Tian X, Xu Z, Li Z, Ma Y, Lian S, Guo X, et al. Pharmacokinetics of mangiferin and its metabolite—norathyriol, part 2: influence of UGT, CYP450, P-gp, and enterobacteria and the potential interaction in *Rhizoma Anemarrhenae* decoction with timosaponin B2 as the major contributor. *Biofactors.* 2016;42(5): 545:555. DOI: https://doi.org/10.1002/biof.1290
47. Gidwani B, Bhairam M, Shukla SS, Verma H, Pandey RK. Herbal bioenhancers in pharmaceutical drug delivery: mechanisms, challenges, and future innovations. *Chem. Biodivers.* 2025;22(9): e00760. DOI: https://doi.org/10.1002/cbdv.202500760
48. de Souza JRR, Feitosa JPA, Ricardo NMPS, Trevisan MTS, de Paula HCB, Ulrich CM, et al. Spray-drying encapsulation of mangiferin using natural polymers. *Food Hydrocoll.* 2013;33(1): 10:18. DOI: https://doi.org/10.1016/j.foodhyd.2013.02.017
49. Khurana RK, Bansal AK, Beg S, Burrow AJ, Katare OP, Singh KK, et al. Enhancing biopharmaceutical attributes of phospholipid complex-loaded nanostructured lipidic carriers of mangiferin: systematic development, characterization and evaluation. *Int J Pharm.* 2017;518(1-2): 289:306. DOI: https://doi.org/10.1016/j.ijpharm.2016.12.044
50. Alkholifi FK, Alam A, Foudah AI, Yusufoglu HS. Phospholipid-based topical nano-hydrogel of mangiferin: enhanced topical delivery and improved dermatokinetics. *Gels.* 2023;9(3):178. DOI: https://doi.org/10.3390/gels9030178
51. Sarfraz M, Khan A, Batiha GE, Akhtar MF, Saleem A, Ajiboye BO, et al. Nanotechnology-based drug delivery approaches of mangiferin: promises, reality and challenges in cancer chemotherapy. *Cancers (Basel).* 2023;15(16):4194. DOI: https://doi.org/10.3390/cancers15164194
52. Baghel M, Baghel I, Kumari P, Bharkatiya M, Joshi G, Sakure K, et al. Nano-delivery systems and therapeutic applications of phytodrug mangiferin. *Appl. Biochem. Biotechnol.* 2024;196(10):7429-63. DOI: https://doi.org/10.1007/s12010-024-04906-6
53. Adin SN, Gupta I, Rashid MA, Alhamhoom Y, Aqil M, Mujeeb M. Nanotransethosomes for enhanced transdermal delivery of mangiferin against rheumatoid arthritis: formulation, characterization, in vivo pharmacokinetic and pharmacodynamic evaluation. *Drug Deliv.* 2023;30(1):2173338. DOI: https://doi.org/10.1080/10717544.2023.2173338
54. Wu JY, Ding HY, Wang TY, Tsai YL, Ting HJ, Chang TS. Improving aqueous solubility of natural antioxidant mangiferin through glycosylation by maltogenic amylase from *Parageobacillus galactosidasius* DSM 18751. *Antioxidants.* 2021;10(11):1733. DOI: https://doi.org/10.3390/antiox10111817
55. Guo H, Chen M, Li M, Hu M, Chen B, Zhou C. Pharmacokinetic comparisons of mangiferin and mangiferin monosodium salt in rat plasma by UPLC-MS/MS. *J Chem.* 2019;2019:2087265. DOI: https://doi.org/10.1155/2019/9272710
56. Lin H, Teng H, Wu W, Li Y, Lv G, Huang X, et al. Pharmacokinetic and metabolomic analyses of mangiferin calcium salt in rat models of type 2 diabetes and non-alcoholic fatty liver disease. *BMC Pharmacol. Toxicol.* 2020;21(1):59. DOI: https://doi.org/10.1186/s40360-020-00438-x
57. Fuentes-Rios D, Sanchez-Rodriguez A, Lopez-Rios L, Garcia-Gonzalez E, Martinez-Canton M, Galvan-Alvarez V, et al.

Human pharmacokinetic profiling and comparative analysis of mangiferin and its monosodium derivative from *Mangifera indica* extracts using UHPLC-MS/MS with ^{1}H NMR and MALDI-TOF confirmation. *Molecules.*2025;30(3):412. DOI: https://doi.org/10.3390/molecules30030461

58. Castellote-Caballero Y, Beltrán-Arranz A, Aibar-Almazán A, Carcelén-Fraile MC, Rivas-Campo Y, López-Rios L, et al. Acute supplementation of soluble mango leaf extract (Zynamite S) improves mental performance and mood: a randomized, double-blind, placebo-controlled crossover study. *Pharmaceuticals.* 2025;18(4):571. DOI: https://doi.org/10.3390/ph18040571
59. Martirosyan DM, Stratton S. Quantum and tempus theories of functional food science in practice. *Funct. Food Sci.* 2023;3(5):55-62. DOI: https://doi.org/10.31989/ffs.v3i5.1122
60. Martirosyan D, Alvarado A. Functional foods regulation system: proposed regulatory paradigm by Functional Food Center. *Funct. Food Sci.* 2023;3(11):210–22. DOI: https://doi.org/10.31989/ffs.v3i11.1265
61. Martirosyan D, Stratton S. Advancing functional food regulation. *Bioact. Compd. Health Dis.* 2023;6(7):153–66. DOI: https://doi.org/10.31989/bchd.v6i7.1178
62. Marecek S, Martirosyan D. An assessment of clinical trials used in functional food science. *Funct. Foods Health Dis.* 2023;13(2):22–35. DOI: https://doi.org/10.31989/ffhd.v13i2.1077
63. Martirosyan D. Functional Food Science and Bioactive Compounds. *Bioact. Compd. Health Dis.* 2025;8(6):218–29. DOI: https://doi.org/10.31989/bchd.v8i6.1667
64. Bermingham KM, Linenberg I, Polidori L, et al. Effects of a personalized nutrition program on cardiometabolic health: a randomized controlled trial. *Nat. Med.* 2024; 30:1888–97. DOI: https://doi.org/10.1038/s41591-024-02951-6
65. Roman S, Campos-Medina L, Leal-Mercado L. Personalized nutrition: the end of the one-diet-fits-all era. *Front. Nutr.* 2024; 11:1370595. DOI: https://doi.org/10.3389/fnut.2024.1370595