



Received on 02 June 2026; received in revised form, 28 June 2026; accepted, 05 July 2026; published 01 November 2026

PLANT-DERIVED PANCREATIC LIPASE INHIBITORS: ETHNOPHARMACOLOGY, PHYTOCHEMISTRY, AND THERAPEUTIC POTENTIAL IN OBESITY

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Keywords:

Obesity, Pancreatic lipase inhibitors, Ethnopharmacology, Phytochemicals, Polyphenols, Structure–activity relationship, Medicinal plants, Functional foods

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ABSTRACT: Obesity affects more than one billion people worldwide, imposing economic burdens projected to exceed \$4 trillion annually by 2035. Pancreatic lipase inhibition represents a mechanistically distinct peripheral approach to obesity management; however, orlistat the sole FDA-approved inhibitor is constrained by severe gastrointestinal adverse effects (>90% incidence), modest efficacy (2.9% placebo-subtracted weight loss), and poor adherence (60-77% discontinuation). Phytochemical alternatives, derived from diverse traditional medicine systems, offer superior tolerability, multi-target mechanisms, and global accessibility. This comprehensive review integrates ethnopharmacological, chemical, and pharmacological perspectives on phytochemical pancreatic lipase inhibitors. Traditional systems Traditional Chinese Medicine, Ayurveda, Indonesian Jamu, Mediterranean herbalism, and beyond demonstrate botanical diversity empirically corroborated by modern validation. Major classes, including polyphenols (flavonoids, catechins, tannins), terpenoids, alkaloids, saponins, carotenoids, and bioactive peptides, exhibit IC₅₀ values from 0.048 μM (oolonghomobisflavan A) to >100 μM. Standouts include galloylated tea catechins, Ginkgo biloba biflavones, and Nelumbo nucifera quercetin derivatives. These agents extend beyond lipase inhibition, modulating α-glucosidase, enriching *Akkermansia muciniphila* in the gut microbiome, suppressing inflammation, and inhibiting adipogenesis. Their limited systemic absorption long considered a limitation optimizes gastrointestinal localization and safety. Phytochemical lipase inhibitors thus fuse ancestral wisdom with scientific rigor, warranting personalized nutrition strategies, advanced delivery systems, untapped biodiversity exploration, and rigorous clinical trials for integration with conventional therapies.

INTRODUCTION:

The Global Obesity Pandemic: A Public Health Crisis: Obesity has evolved from a condition of affluence to a global pandemic affecting both developed and developing nations, representing one

of the most pressing public health challenges of the 21st century¹. Obesity affects more than one billion people globally. With rising prevalence, the World Obesity Federation projects the annual economic burden will exceed \$4 trillion by 2035 if trends continue unchecked²⁻⁴.

Obesity is intrinsically linked to type 2 diabetes, cardiovascular disease, certain cancers, and reduced life expectancy, profoundly impacting quality of life and healthcare systems⁵⁻⁷. Obesity induces metabolic dysfunction, while associated

<p>QUICK RESPONSE CODE</p>  <p>DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(11).3267-91</p>	<p>DOI: 10.13040/IJPSR.0975-8232.17(11).3267-91</p> <hr/> <p>This article can be accessed online on www.ijpsr.com</p>
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comorbidities further limit physical activity and perpetuate weight gain^{8,9}. The etiology of obesity is multifactorial, involving complex interactions among genetic predisposition, environmental factors, dietary patterns, sedentary lifestyles, socioeconomic determinants, and the modern obesogenic environment¹⁰⁻¹³.

The modern obesogenic environment energy-dense processed foods, sedentary urban design, screen entertainment demands conscious effort to maintain healthy weight rather than natural occurrence¹⁴.

Pharmacotherapy: Promise, Peril, and the Quest for Safer Alternatives: Despite obvious medical necessity, obesity pharmacotherapy has been characterized by a troubled history of promising beginnings followed by safety-driven withdrawals¹⁵. Numerous anti-obesity agents have been approved and subsequently withdrawn due to serious safety concerns, particularly cardiovascular and psychiatric adverse effects associated with centrally-acting appetite suppressants affecting catecholaminergic and serotonergic pathways¹⁶. The litany of withdrawn medications fenfluramine, sibutramine, rimonabant serves as a sobering reminder that intervention in complex homeostatic systems carries inherent risks¹⁷.

The recent emergence of glucagon-like peptide-1 (GLP-1) receptor agonists has revolutionized obesity treatment. GLP-1 receptor agonists have transformed obesity treatment, producing weight reductions exceeding 15–20% in clinical trials¹⁸. However, their widespread use is limited by high cost, injectable administration, gastrointestinal adverse effects, weight regain after discontinuation, and uncertainties regarding long-term safety¹⁹. Limited accessibility further restricts their use in many populations most affected by obesity²⁰.

Peripheral nutrient absorption inhibitors represent a mechanistically distinct approach by reducing dietary fat absorption within the gastrointestinal tract, thereby promoting weight loss while minimizing the cardiovascular and psychiatric risks associated with centrally acting agents^{17, 21-23}.

Orlistat: Lessons from the Only Approved Lipase Inhibitor: Orlistat (tetrahydrolipstatin), a semi-synthetic derivative of the bacterial natural product lipstatin, remains the sole FDA-approved

pancreatic lipase inhibitor since 1999^{22, 24}. By covalently and irreversibly inhibiting pancreatic and gastric lipases, orlistat reduces dietary fat absorption by approximately 30% at the recommended dose of 120 mg three times daily with meals²⁵.

Despite proven efficacy, orlistat's long-term use is limited by gastrointestinal adverse effects including steatorrhea, fecal urgency, oily spotting, and flatulence reported in up to 91% of treated patients owing to unabsorbed dietary fat reaching the colon.^{26, 27}. These adverse effects contribute substantially to poor treatment adherence, with real-world discontinuation rates exceeding 60%²⁸. Weight reduction is also modest, averaging 2–3 kg greater than placebo over one year (approximately 2.9% placebo-subtracted weight loss), substantially lower than that achieved with GLP-1 receptor agonists²⁹. Additional limitations include impaired absorption of fat-soluble vitamins and rare reports of hepatotoxicity. Although orlistat validates pancreatic lipase as a clinically relevant therapeutic target, its limitations underscore the need for safer, better-tolerated, and more acceptable plant-derived lipase inhibitors.

The Phytochemical Alternative: Ancient Wisdom Meets Modern Science: For millennia, traditional medical systems including Traditional Chinese Medicine, Ayurveda, and Indonesian Jamu used plant-based remedies to manage conditions now recognized as obesity and metabolic disorders³⁰. These empirically-derived approaches, refined through countless generations, represent an invaluable repository of bioactive chemistry awaiting systematic investigation.

Phytochemicals further offer structural diversity, multi-target mechanisms, favorable safety profiles, cultural acceptance, and affordability, making them attractive candidates for obesity management³¹.

Recent technological advances have accelerated phytochemical discovery: high-resolution mass spectrometry enables comprehensive metabolomic profiling; molecular docking predicts binding modes with remarkable accuracy; bioassay-guided fractionation efficiently isolates active principles^{32, 33}. These tools transform traditional medicine from empirical practice into evidence-based science,

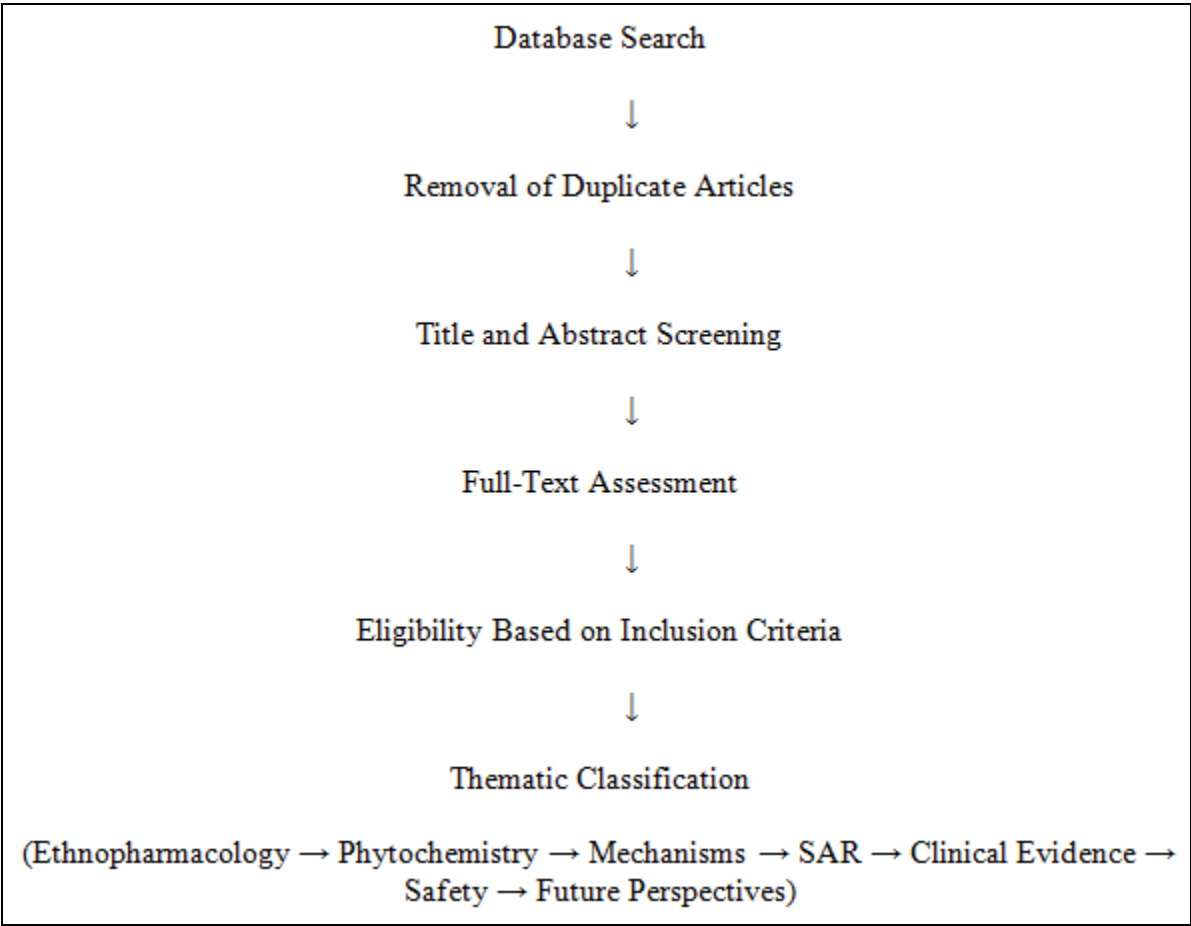
bridging ancestral knowledge with contemporary therapeutic development³⁴.

Review Methodology: This narrative review provides a comprehensive overview of plant-derived pancreatic lipase inhibitors, focusing on their ethnopharmacological relevance, phytochemistry, mechanisms of action, structure activity relationships, pharmacological evidence, safety, and translational potential in obesity management. A structured literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Google Scholar, and SpringerLink, supplemented by authoritative books and the reference lists of relevant publications. The review primarily considered studies published between 2000 and June 2026, while earlier landmark reports on pancreatic lipase, orlistat, traditional medicine, and key phytochemicals were

included where scientifically relevant. Search terms included obesity, pancreatic lipase, lipase inhibitors, phytochemicals, medicinal plants, ethnopharmacology, polyphenols, flavonoids, terpenoids, alkaloids, bioactive peptides, traditional medicine, Ayurveda, Traditional Chinese Medicine, Jamu, and structure–activity relationship.

Eligible literature comprised peer-reviewed original research articles, reviews, ethnopharmacological surveys, phytochemical studies, molecular docking investigations, *in-vitro* and *in-vivo* studies, clinical trials, systematic reviews, and meta-analyses. Publications providing experimentally validated pancreatic lipase inhibitory activity, phytochemical characterization, mechanistic insights, or clinically relevant evidence were prioritized.

Workflow for Review Methodology:



Ethnopharmacological Perspectives:

Traditional Medicine and Anti-Obesity Botanicals:

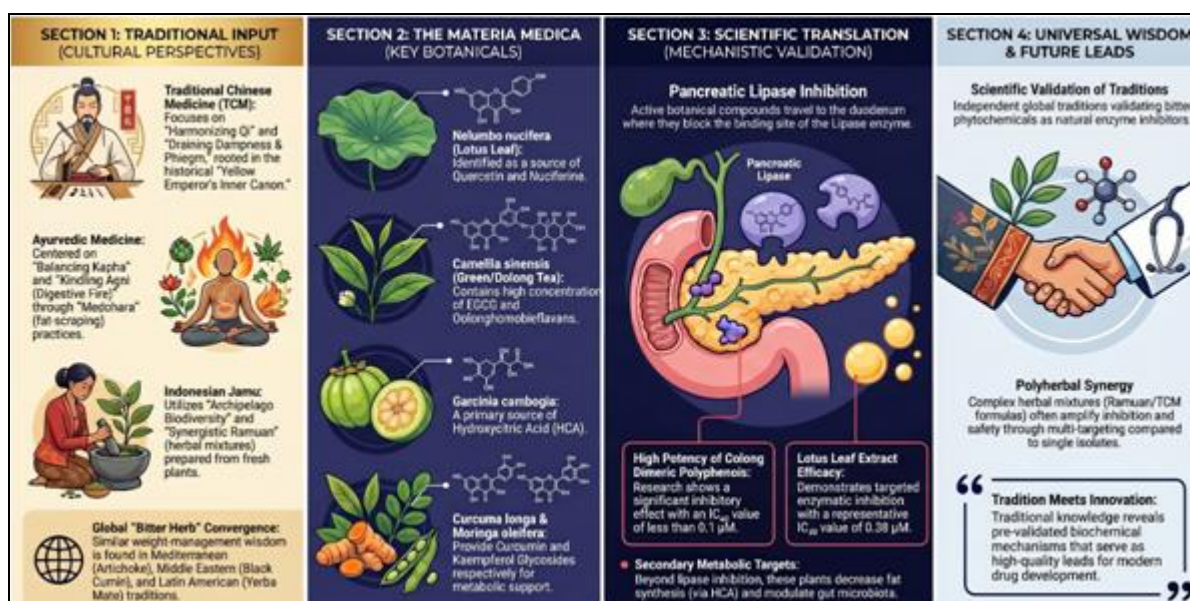


FIG. 1: TRADITIONAL MEDICINE & ANTI-OBESITY: GLOBAL BOTANICAL CONVERGENCE

Asian Traditional Medicine Systems: A Rich Botanical Heritage:

Traditional Chinese Medicine: Harmonizing Qi and Draining Dampness: Traditional Chinese Medicine (TCM) attributes obesity to imbalances in Qi and the accumulation of dampness and phlegm, concepts that broadly correspond to metabolic dysfunction and lipid accumulation in modern medicine^{35–38}.

Among TCM's extensive materia medica, *Nelumbo nucifera* (sacred lotus) stands as the paradigmatic anti-obesity botanical. Prescribed for over 1,300 years to "drain dampness, promote diuresis, and reduce turbidity," lotus leaf extracts demonstrate spectacular validation: potent pancreatic lipase inhibition with IC_{50} values as low as $0.38 \mu\text{M}$, attributed to quercetin, myricetin, and alkaloids including nuciferine³⁹. This correlation between traditional "dampness-draining" properties and contemporary lipase inhibition exemplifies how systematic investigation of empirical observation reveals biochemical mechanisms⁴⁰.

Camellia sinensis (tea plant) represents another TCM cornerstone, with green, oolong, and black tea consumed therapeutically for centuries to "digest food accumulation and transform fat," particularly after fatty meals^{41, 42}. Modern research confirms that galloylated catechins—especially (-)-epigallocatechin-3-gallate (EGCG)—potently inhibit pancreatic lipase through competitive mechanisms⁴³. Oolong tea's traditional weight

management use finds molecular support in unique dimeric polyphenols (oolonghomobisflavans) exhibiting IC_{50} values below $0.1 \mu\text{M}$,^{44, 45}.

Other TCM botanicals, including *Rheum palmatum* and *Glycyrrhiza spp.*, also exhibit pancreatic lipase inhibitory activity through anthraquinones, polyphenols, and chalcone derivatives, further supporting the diversity of anti-obesity phytochemicals used in TCM^{46, 47}.

Ayurvedic Medicine: Balancing the Doshas:

Ayurveda attributes obesity (*Sthaulya* or *Medoroga*) primarily to aggravated *Kapha* dosha and impaired metabolic function (*Agni*), with treatment focused on *Medohara* (fat-reducing) herbs that restore metabolic balance^{48–50}.

Among these, *Garcinia cambogia* is one of the most extensively used anti-obesity botanicals. Traditionally prescribed to enhance satiety and reduce fat accumulation, its principal constituent, hydroxycitric acid (HCA), inhibits ATP-citrate lyase, while recent studies also demonstrate pancreatic lipase inhibitory activity^{51–54}.

Similarly, *Curcuma longa* and *Curcuma xanthorrhiza* are widely used in Ayurvedic medicine for weight management. In addition to their anti-inflammatory and metabolic effects, turmeric extracts exhibit pancreatic lipase inhibitory activity, supporting their traditional *Medohara* classification^{55, 56}. *Trigonella foenum-graecum* (fenugreek, *Methi*) seeds contain saponins

and polyphenols exhibiting lipase inhibitory properties alongside documented effects on glucose metabolism and satiety^{57, 58}.

Collectively, these findings provide experimental support for traditional Ayurvedic anti-obesity formulations and highlight their potential as sources of plant-derived pancreatic lipase inhibitors⁵⁹.

Indonesian Jamu: Island Botanical Wisdom: Indonesian traditional medicine (Jamu) utilizes diverse botanical preparations for weight management, several of which have subsequently demonstrated experimentally validated pancreatic lipase inhibitory activity^{31, 60}.

Moringa oleifera is among the best-characterized Jamu anti-obesity plants. Leaf extracts, rich in quercetin and kaempferol glycosides, exhibit pancreatic lipase inhibitory activity together with anti-inflammatory effects and modulation of the gut microbiota, supporting its traditional use for weight management^{61, 62}.

Similarly, *Kaempferia angustifolia* demonstrates pancreatic lipase inhibition, suppression of adipogenesis, and regulation of lipid metabolism, whereas *Tamarindus indica* provides hydroxycitric acid and polyphenols with validated lipase inhibitory activity, illustrating the integration of food and medicine characteristic of Jamu formulations^{31, 60}.

Other Regional Systems: Global Botanical Convergence:

Mediterranean Traditional Practices: Mediterranean traditional medicine, influenced by Greco-Roman, Arabic, and indigenous European practices, emphasizes dietary modification and specific botanicals for corpulence⁶³. Olive leaf (*Olea europaea*) extracts, traditionally consumed as infusions for metabolic health, demonstrate pancreatic lipase inhibition attributed to oleuropein and related secoiridoid compounds⁶⁴. Artichoke (*Cynara scolymus*) leaf preparations, used traditionally to aid digestion of fatty meals, exhibit lipase inhibitory activity alongside their documented choloretic effects. The Mediterranean practice of consuming bitter herbs before meals including chicory, dandelion, and gentian aligns

with modern findings that bitter phytochemicals often possess enzyme inhibitory properties^{65, 66}.

Middle Eastern and Arabic Medicine: Arabic traditional medicine (*Unani-Tibb*), synthesizing Greco-Roman, Persian, and Indian influences, classifies obesity as resulting from excessive "moisture" and "heat" imbalances⁶⁷. *Nigella sativa* (black cumin),⁶⁸ prescribed for numerous metabolic conditions, demonstrates pancreatic lipase inhibition alongside anti-inflammatory and insulin-sensitizing effects^{69, 70}. Pomegranate (*Punica granatum*) peel and seed preparations, traditionally used for digestive disorders and obesity, contain ellagitannins and other polyphenols with validated lipase inhibitory activity. The Arabic medical tradition's emphasis on dietary spices—including cumin, coriander, and cinnamon—for metabolic health finds support in modern demonstrations of lipase inhibition by spice-derived phytochemicals⁷¹.

Latin American Ethnomedicine: Indigenous Latin American medical traditions employ numerous botanicals for weight management, many unexplored by modern science⁷². *Ilex paraguariensis* (yerba mate), consumed traditionally throughout South America for energy and appetite control, contains caffeoylquinic acids and saponins demonstrating pancreatic lipase inhibition⁷³. Nopal cactus (*Opuntia* species) mucilage and polyphenols, used traditionally in Mexico for diabetes and obesity, exhibit multi-target metabolic effects including lipase inhibition. The traditional practice of consuming bitter Amazonian botanicals for "cleansing" and weight reduction awaits systematic investigation for lipase inhibitory potential⁷⁴.

African Traditional Medicine: African ethnomedicine's rich botanical heritage includes numerous anti-obesity plants deserving investigation. *Hibiscus sabdariffa* (roselle) calyx preparations, consumed across Africa for various metabolic conditions, demonstrate pancreatic lipase inhibition attributable to anthocyanins and organic acids^{75, 76}. *Hoodia gordonii*, traditionally used by San peoples as an appetite suppressant during hunting expeditions, gained commercial attention for its steroidal glycoside P57, though pancreatic lipase effects remain underexplored⁷⁷.

The traditional practice in various African cultures of consuming bitter leaf vegetables (*Vernonia amygdalina* and others) with fatty meals suggests empirical recognition of enzyme inhibitory properties.

Common Themes Across Cultures: Universal Botanical Wisdom: Despite marked geographical and cultural differences, traditional medical systems show remarkable convergence in their botanical approaches to obesity management. Across diverse traditions, bitter medicinal plants rich in polyphenols, terpenoids, and related phytochemicals were consistently employed for weight management, many of which have subsequently demonstrated pancreatic lipase inhibitory activity and other metabolically relevant effects³¹.

Another common feature is the widespread use of multi-herb formulations. Traditional Chinese Medicine, Ayurveda, Jamu, and Mediterranean and Arabic medical systems all employ polyherbal preparations, which may enhance therapeutic efficacy through complementary phytochemicals acting on multiple metabolic targets. These shared ethnopharmacological principles have provided valuable leads for the modern discovery of plant-derived pancreatic lipase inhibitors.

Representative medicinal plants used across traditional medical systems, together with their major phytoconstituents and experimental evidence for pancreatic lipase inhibition, are summarized in **Table 1**.

TABLE 1:

Traditional System	Representative Plant (Part Used)	Major Active Phytoconstituent(s)	Experimental Validation	Ref
TCM	<i>Nelumbo nucifera</i> (Leaf) <i>Camellia sinensis</i> (Leaf)	Quercetin, myricetin, nuciferine; EGCG, oolonghomobisflavans	<i>In-vitro</i> (PPL); IC ₅₀ = 0.38 μM; competitive inhibition	39, 45
Ayurveda	<i>Garcinia cambogia</i> (Fruit rind) <i>Curcuma longa</i> (Rhizome)	Hydroxycitric acid; Curcuminoids	<i>In-vitro/In-vivo</i> ; pancreatic lipase inhibition; multi-target effects	53, 55
Jamu	<i>Moringa oleifera</i> (Leaf) <i>Tamarindus indica</i> (Fruit)	Quercetin, kaempferol; Polyphenols	<i>In-vitro</i> ; validated pancreatic lipase inhibition	65, 78
Mediterranean	<i>Olea europaea</i> (Leaf) <i>Cynara scolymus</i> (Leaf)	Oleuropein; Cynarin	<i>In-vitro</i> ; pancreatic lipase inhibition	64, 65
Arabic	<i>Nigella sativa</i> (Seed) <i>Punica granatum</i> (Peel/Seed)	Thymoquinone; Ellagitannins	<i>In-vitro/In-vivo</i> ; pancreatic lipase inhibition	68, 75
Latin American	<i>Ilex paraguariensis</i> (Leaf) <i>Opuntia</i> spp. (Cladode)	Caffeoylquinic acids; Polyphenols	Validated anti-obesity activity including pancreatic lipase inhibition	73, 74
African	<i>Hibiscus sabdariffa</i> (Calyx) <i>Hoodia gordonii</i> (Stem)	Anthocyanins; P57 glycoside	Lipase inhibition reported; appetite suppression (Hoodia)	75, 77

Experimental evidence is based on representative published studies. Variations in assay conditions, pancreatic lipase source, substrate, and extract preparation may influence the reported inhibitory activity. Detailed descriptions are provided in Sections 3.1–3.2 and the cited references

From Empiricism to Evidence: Validating Traditional Knowledge:
Ethnopharmacological Validation of Traditional Anti-obesity Botanicals: The scientific investigation of traditionally used anti-obesity plants has provided substantial support for ethnopharmacological knowledge, identifying numerous phytochemicals with experimentally validated pancreatic lipase inhibitory activity.

Nelumbo nucifera represents one of the best-characterized examples. Traditionally used in Traditional Chinese Medicine for obesity and digestive disorders, lotus leaves contain flavonoids and alkaloids, including quercetin, myricetin, and nuciferine, which exhibit potent pancreatic lipase inhibitory activity (IC₅₀ as low as 0.38 μM)^{79–81}. Similarly, *Camellia sinensis* demonstrates how traditional processing methods influence biological

activity. Differences in green, oolong, and black tea processing alter catechin composition and galloylation patterns, resulting in distinct pancreatic lipase inhibitory profiles. Oolong tea polyphenols, particularly oolonghomobisflavans, exhibit potent inhibitory activity^{45, 82, 83}.

Comparable anti-obesity plants identified independently in geographically distinct traditional medical systems, including *Garcinia* species, frequently share similar phytochemical constituents and mechanisms of action, highlighting the value of ethnopharmacological knowledge in guiding the discovery of plant-derived pancreatic lipase inhibitors.

The Reverse Pharmacology and Ethnopharmacological Drug Discovery: Reverse pharmacology validates traditional medicine by starting with long-standing human use and progressing through ethnobotanical study, phytochemical analysis, mechanism investigation, and clinical testing. This approach inverts conventional drug discovery by treating centuries of use as pre-screening. In obesity, it offers key advantages: proven safety from widespread historical consumption, cultural acceptance, and faster translation into dietary supplements or functional foods due to less stringent regulatory requirements than new synthetic drugs⁸⁴⁻⁸⁶.

Ethnobotanical surveys have documented numerous medicinal plants with traditional anti-obesity applications across Asian, African, and Latin American medical systems⁸⁷. Bioprospecting guided by traditional knowledge demonstrates significantly higher hit rates (10-30%) in bioactivity screening versus random plant collection (<1%), underscoring ethnopharmacological information's value⁸⁷.

Modern analytical techniques, including high-resolution mass spectrometry, nuclear magnetic resonance spectroscopy, and metabolomics, facilitate comprehensive characterization of traditional botanical preparations and support the development of standardized, quality-controlled phytopharmaceuticals

Intellectual Property, Equity, and Sustainability: The commercialization of traditional medicinal knowledge raises important

ethical considerations regarding recognition of indigenous communities and equitable benefit-sharing, as emphasized by the Nagoya Protocol⁸⁹.

Sustainable sourcing is equally critical. Overharvesting of high-demand species such as *Hoodia gordonii* and *Garcinia cambogia* has caused population declines and local ecological damage, underscoring the need for cultivation, defined sustainable harvesting, and conservation programs as traditional remedies enter global markets. Development of phytochemical lipase inhibitors must therefore align therapeutic innovation with respect for knowledge holders, regulatory compliance, environmental stewardship, and equitable benefit-sharing⁹⁰.

Ethnopharmacology provides a strong foundation for this work, combining diverse medical traditions, long-term empirical use, and increasing scientific validation. Traditional systems have already identified plants with genuine anti-obesity activity, offering pre-validated leads for modern drug, nutraceutical, and functional food development. The following sections examine their phytochemistry, mechanisms, and translational potential as evidence-based interventions⁹¹.

Phytochemical Classes as Pancreatic Lipase Inhibitors:

Polyphenolic Compounds: Diversity and Potency: Polyphenolic compounds represent the most extensively studied phytochemical class for pancreatic lipase inhibition, encompassing structurally diverse molecules unified by multiple aromatic rings bearing hydroxyl substituents⁹². This chemical diversity translates to varied inhibitory mechanisms, binding modes, and potencies ranging from micromolar to nanomolar IC₅₀ values. Polyphenols' abundance in human diets—particularly in fruits, vegetables, teas, and medicinal herbs—positions them uniquely as both therapeutic agents and preventive nutritional components⁹³.

Flavonoids: The Predominant Inhibitor Class: Flavonoids, characterized by a C6-C3-C6 carbon skeleton comprising two aromatic rings (A and B) connected by a three-carbon bridge forming a heterocyclic C ring, constitute the largest and most potent group of natural lipase inhibitors. Subtle

structural variations hydroxylation patterns, glycosylation, methylation, prenylation dramatically influence inhibitory activity, creating a rich structure-activity landscape^{92, 94}.

Flavones and Flavonols: Planar π -Systems:

Among 26 flavonoids tested, flavones exhibited strongest inhibitory activity: luteolin (IC_{50} 99 ± 11 μ M), quercetin (IC_{50} 128 ± 22 μ M), and baicalein (IC_{50} 156 ± 22 μ M). Structure-activity relationships reveal critical determinants: C2=C3 double bond and C4 carbonyl in the C ring are essential—hydrogenation or carbonyl removal significantly decreases activity; hydroxylation on rings A and B enhances potency, while glycosylation typically weakens it^{92, 94}.

The C2=C3 double bond confers planarity enabling optimal π - π stacking with aromatic active site residues, particularly Phe77⁹⁴. Quercetin demonstrates variable potency across studies (IC_{50} 1.5-128 μ M) reflecting assay condition dependencies substrate type, enzyme source, pH, colipase presence underscoring standardized methodology's importance. Recent studies identified myricetin and quercetin as potent inhibitors (IC_{50} ~ 1.5 μ M), suggesting optimized conditions reveal higher intrinsic potency⁹⁵.

Baicalein (5,6,7-trihydroxyflavone) merits special attention: its A-ring pyrogallol group constitutes a key lipase inhibition motif. Rational 4'-position modification yielded remarkable improvements: 4'-amino baicalein (ABA) and 4'-pyrrolidine baicalein (PBA) emerged as novel potent inhibitors (IC_{50} < 1 μ M), representing >150 -fold enhancement. This exemplifies how systematic structure-based optimization achieves near-synthetic drug potencies while retaining favorable natural product characteristics^{96, 97}.

Glycosylation effects depend critically on sugar identity and attachment position. Kaempferol-3-O-rutinoside exhibited highest activity (IC_{50} 2.9 μ M), while rutin, quercetin, and luteolin showed weak inhibition (IC_{50} >100 μ M), indicating specific disaccharide configurations can enhance activity through favorable binding site interactions⁹⁸.

Biflavones: Dimeric Potency: Biflavones—dimeric flavonoids connected through C-C or C-O-C linkages—occur predominantly in gymnosperms

(Ginkgo, Araucaria) and certain angiosperms. Major biflavones from *Ginkgo biloba* including isoginkgetin, bilobetin, ginkgetin, and sciadopitysin displayed strong to moderate pancreatic lipase inhibition with IC_{50} values ranging from 2.90 to 12.78 μ M, with K_i values below 2.5 μ M for isoginkgetin, bilobetin, and ginkgetin, indicating tight-binding competitive inhibition⁹⁹. The enhanced potency of biflavones versus monomeric flavonoids likely reflects their capacity to span larger binding site regions, simultaneously interacting with both the catalytic machinery and substrate-binding tunnel through their extended structures⁹⁴.

Polymethoxylated Flavones: Citrus Specialties:

Polymethoxylated flavones (PMFs), abundant in citrus peels, bear multiple methoxy substituents that enhance lipophilicity and potentially improve gastrointestinal retention. Nobiletin (5,6,7,8,3',4'-hexamethoxyflavone) demonstrated superior pancreatic lipase inhibition with IC_{50} 3.60 ± 0.19 μ M compared to other PMFs tested, suggesting that the specific methoxylation pattern—particularly the 3'-methoxy group—optimizes binding interactions¹⁰⁰. The increased lipophilicity of PMFs may facilitate membrane interactions and local concentration at the lipid-water interface where lipase operates, potentially contributing to their potency beyond direct enzyme binding¹⁰¹.

Flavan-3-ols and Galloylated Catechins: Tea Polyphenol Paradigms:

Tea (*Camellia sinensis*) polyphenols, particularly catechins and their galloylated derivatives, represent extensively characterized lipase inhibitors with well-documented structure-activity relationships.^[45] Non-esterified flavan-3-ols including (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin showed negligible activity against pancreatic lipase (IC_{50} >20 μ M),^{102, 103} while the presence of galloyl moieties within the structure was required for enhanced inhibition.

This galloylation dependence exhibits clear dose-response characteristics: (-)-epigallocatechin 3-O-gallate (EGCG), containing one galloyl moiety, showed lipase inhibition with IC_{50} 0.349 μ M, while flavan-3-ol digallate esters such as (-)-epigallocatechin-3,5-digallate demonstrated even higher activity with IC_{50} 0.098 μ M⁴⁵.

This nearly 4-fold potency enhancement from monogallate to digallate underscores the galloyl group's critical contribution—likely through additional hydrogen bonding with active site residues and enhanced hydrophobic interactions¹⁰⁴ via the galloyl aromatic ring.

Comparative analysis of phenolic compounds confirms galloyl ester superiority: Among tested phenolics, only gallic acid (IC₅₀ 387.2 μ M), epigallocatechin (EGC, IC₅₀ 237.3 μ M), and EGCG (IC₅₀ 391.2 μ M) showed comparative pancreatic lipase inhibition¹⁰⁵. The mechanistic basis involves competitive inhibition, with galloyl esters binding within the active site¹⁰⁶ and preventing substrate access.

Oolong Tea Polyphenols: Fermentation-Enhanced Activity: Oolong tea, produced through partial fermentation creating unique oxidative coupling products, exhibits exceptional lipase inhibitory properties. Oolong tea polymerized polyphenols (OTPP) showed 5-fold stronger inhibition (IC₅₀ 0.28 μ g/mL) compared to tannase-treated OTPP (IC₅₀ 1.38 μ g/mL), confirming that polymerization and esterification enhance activity. Remarkably, oolonghomobisflavan A and B, and oolongtheanin 3'-O-gallate—compounds characteristic of oolong tea—demonstrated IC₅₀ values of 0.048, 0.108, and 0.068 μ M respectively, surpassing even EGCG, and approaching orlistat's potency range (IC₅₀ 0.092 μ M)^{45, 106}.

These dimeric theasinensins represent fermentation-generated structures unavailable in unprocessed tea, exemplifying how traditional processing methods create novel bioactive chemistry. Their nanomolar potencies position them among the most potent natural lipase inhibitors identified, warranting development as standardized extracts or purified compounds for obesity management.

Other Polyphenolic Inhibitors: Structural Diversity:

Phenolic Acids: Weak but Ubiquitous: Simple phenolic acids generally exhibit weaker lipase inhibition than complex polyphenols. Caffeic acid, p-coumaric acid, and related hydroxycinnamic acids show IC₅₀ values typically exceeding 100 μ M, though they contribute to the overall activity

of plant extracts and may exhibit synergistic effects in combination. Gallic acid (3,4,5-trihydroxybenzoic acid) demonstrated IC₅₀ 387.2 μ M,⁴⁵ representing moderate activity among simple phenolics. The trihydroxybenzene (pyrogallol) motif appears beneficial across compound classes,¹⁰⁷ consistent with observations for baicalein and galloylated catechins¹⁰⁸.

Stilbenes and Curcuminoids: Stilbenes, characterized by a C6-C2-C6 skeleton with a trans-double bond connecting aromatic rings, occur notably in grapes, berries, and Polygonaceae¹⁰⁹. While resveratrol receives extensive attention for cardiovascular and anti-aging properties, its pancreatic lipase inhibitory activity remains modest¹¹⁰. *Oligomeric stilbenes* (viniferins) from grapevine may possess enhanced activity through mechanisms analogous to biflavone potency enhancement, though systematic investigation is limited¹⁰⁹.

Curcuminoids from turmeric (*Curcuma longa*) demonstrate multi-target anti-obesity effects including lipase inhibition, though potencies (IC₅₀ 50-200 μ M) lag behind flavonoids¹¹¹. Their value lies in pleiotropic mechanisms---anti-inflammatory activity, adipogenesis suppression, gene regulation---complementing direct enzyme inhibition¹¹².

Tannins: Protein-Binding Polyphenols: Tannins—hydrolyzable (gallic/ellagic acid polymers) or condensed (proanthocyanidins)—interact promiscuously with proteins through hydrogen bonds and hydrophobic interactions. While potentially potent lipase inhibitors, tannins' non-selective protein binding raises concerns about protein digestibility and nutrient absorption. Condensed tannins from *Araucaria angustifolia* demonstrate pancreatic lipase inhibition, though the balance between beneficial lipase inhibition and detrimental nutritional effects must inform therapeutic development^{76, 107}.

Other Phytochemical Classes:

Terpenoids and Saponins: Lipophilic Modulators: Terpenoids, derived from isoprene units (C5) forming diverse structures (monoterpenes C10, sesquiterpenes C15, diterpenes C20, triterpenes C30, tetraterpenes C40), contribute to essential oils and plant resins. Diterpenoids from

Sibiraea angustata demonstrate pancreatic lipase inhibitory activity, though potencies generally lag behind polyphenols¹¹³. Nutmeg-derived tetrahydrofuran compounds represent novel aspects of terpenoid lipase inhibition¹¹⁴, warranting further structural characterization and optimization¹¹⁵.

Triterpenoid saponins—glycosylated triterpenes exhibiting surfactant properties—occur abundantly in legumes, ginseng, and quinoa. Their amphiphilic nature enables membrane interactions and potential interference with lipid emulsification or lipase-colipase complex formation¹¹⁶. Saponins from *Trigonella foenum-graecum* (fenugreek) and *Panax ginseng* contribute to traditional anti-obesity formulations, though distinguishing direct lipase inhibition from indirect effects on lipid digestion¹¹⁷ (emulsification disruption, micellar solubilization) requires careful mechanistic study.

Alkaloids: Nitrogen-Containing Bioactives: Plant alkaloids heterocyclic nitrogen-containing secondary metabolites encompass extraordinary structural diversity. *Nelumbo nucifera* alkaloids including nuciferine complement the lotus leaf's flavonoid content, potentially contributing synergistically to overall lipase inhibition. *Piper* species (black pepper, betel) contain piperine and related alkaloids demonstrating metabolic effects, though direct pancreatic lipase inhibition appears modest^{118, 119}.

Methylxanthines caffeine, theophylline, theobromine from tea, coffee, cocoa represent unique alkaloid lipase modulators¹⁰⁵. While not potent direct inhibitors, they may influence lipid metabolism through adenosine receptor antagonism, phosphodiesterase inhibition, and metabolic rate enhancement, complementing the polyphenol-mediated lipase inhibition in caffeinated beverages^{120, 121}.

Bioactive Peptides: Emerging Protein-Derived Inhibitors: An emerging and underexplored area involves bioactive peptides—short amino acid sequences (typically 2-20 residues) released from food proteins through enzymatic hydrolysis, fermentation, or gastrointestinal digestion¹²². Recent systematic reviews identified 176 bioactive peptides with pancreatic lipase inhibitory activity from diverse sources¹²³ including plant proteins

(millet, rice bran, chickpea, cumin), marine organisms (sea cucumber, tuna, microalgae), and even insects (silkworm pupae).

Plant-derived peptides from legumes¹²⁴ demonstrate IC₅₀ values ranging from 0.5 to 5 mg/mL, with activity depending on amino acid composition—particularly aromatic residues (Phe, Tyr, Trp) that facilitate hydrophobic binding interactions¹²⁵. Marine peptides, rich in unique amino acids and modified residues, exhibit comparable or superior potencies¹²⁶. The peptide mechanism likely involves competitive inhibition through binding near or within the active site, with specific sequences recognized by the enzyme's substrate binding machinery.

Bioactive peptides offer advantages including predictable enzymatic release from dietary proteins, potential for rational design and synthesis, and digestibility limiting systemic absorption (favorable for GI-localized action)¹²³. However, peptides face stability challenges from gastric and pancreatic proteases, requiring formulation strategies (encapsulation, protease inhibitor co-administration, chemical modification) to preserve activity through the upper GI tract¹²⁷.

Carotenoids and Marine Phytochemicals: Fucoxanthin, a marine carotenoid abundant in brown seaweeds (kelp, wakame), demonstrates anti-obesity properties¹²⁸ through multiple mechanisms including lipase inhibition, adipocyte differentiation suppression, and mitochondrial uncoupling protein upregulation^{129, 130}. While fucoxanthin's direct lipase inhibitory potency is moderate, its metabolite fucoxanthinol exhibits enhanced activity. Marine sources—algae,¹³¹ seaweeds, marine bacteria—represent underexplored reservoirs of lipase modulators, with unique halogenated compounds and sulfated polysaccharides warranting systematic investigation.

Chitosan, a deacetylated chitin derivative from crustacean shells, demonstrates fat-binding properties through ionic interactions between positively-charged amino groups and negatively-charged fatty acids¹³². While not a classical enzyme inhibitor, chitosan's capacity to sequester dietary fat and prevent lipase access creates

functional lipase inhibition, supporting its use in weight management supplements¹³³.

Structure-Activity Relationships: Unifying Principles: Despite phytochemical diversity, certain SAR principles emerge consistently across compound classes, providing frameworks for rational optimization and prediction:

Hydroxylation and Hydrogen Bonding: Multiple hydroxyl groups, particularly in clustered arrangements (pyrogallol, catechol motifs), enhance lipase inhibition through hydrogen bonding with the catalytic triad (Ser152, His263, Asp176) and oxyanion hole (Phe77, Leu153), though excessive hydroxylation decreases activity by increasing hydrophilicity^{134, 135}.

Aromatic Systems and π -Interactions: Planar aromatic systems enable π - π stacking with Phe77, Phe215, and Tyr114 lining the active site. The C2=C3 double bond maintains planarity crucial for optimal orientation, while preserving planarity generally enhances binding⁴⁵.

Lipophilicity and Interface Partitioning: Moderate lipophilicity (LogP 2-5) appears optimal, enabling both aqueous solubility for enzyme transport and lipid interface partitioning where lipase functions¹³⁶. Extremely polar compounds fail to reach the lipid-water interface; excessively lipophilic compounds may aggregate or partition entirely into lipid phase¹³⁷. The "Goldilocks zone" balances these competing factors.

Galloylation and Esterification: Galloyl ester moieties dramatically enhance potency across compound classes through the galloyl aromatic ring's π -interactions and additional hydrogen bonding from its three hydroxyl groups, with digallates exceeding monogallates¹⁰⁴.

Molecular Size and Flexibility: Dimeric and oligomeric compounds (biflavones, condensed tannins, oolong tea dimers) often demonstrate superior potencies versus monomers by occupying larger binding site volumes and achieving multivalent interactions, though excessive size may impede binding site access^{45, 99}.

Glycosylation Effects: Sugar attachments generally decrease activity by increasing polarity and molecular size. However, specific glycosylation patterns (e.g., kaempferol-3-O-rutinoside) can enhance activity through favorable interactions with binding site periphery, necessitating empirical evaluation¹³⁸⁻¹⁴⁰.

Table 2 consolidates these SAR principles with mechanistic details, representative examples, and optimal parameter ranges. These principles, derived primarily from polyphenols, likely extend to other classes—terpenoids, alkaloids, and peptides exhibiting lipase inhibition generally possess aromatic character, hydrogen bonding capacity, and moderate lipophilicity, supporting universal binding requirements transcending specific chemical scaffolds.

TABLE 2: STRUCTURE-ACTIVITY RELATIONSHIP PRINCIPLES FOR PANCREATIC LIPASE INHIBITION

Structural Feature	Effect	Mechanism & Example	Optimal Range	Ref.
C2=C3 Double Bond + C4 Carbonyl	↑↑↑ Essential	Planarity for π - π stacking (Phe77); H-bonding Quercetin (active) vs. dihydroquercetin (inactive)	Must be present	[91]
Hydroxylation	↑↑ Enhances ↓ Excessive	H-bonding with Ser152, His263, Asp176, oxyanion hole Pyrogallol motif (baicalein) optimal	3-6 OH groups	[91,95]
Galloylation	↑↑↑ Dramatic (4-350×)	Galloyl aromatic π -interactions + 3 OH H-bonds EGCG (0.349 μ M) >> EC (>20 μ M); Digallates>monogallates	1-2 galloyl groups	[45,103]
Dimerization	↑↑↑ Superior	Multivalent binding, larger footprint Oolonghomobisflavans (0.048 μ M), biflavones (2.9 μ M)	Dimeric preferred	[45,98]
Glycosylation	↓ Generally ↑ Exception	↑ Polarity/size hinders access; rare favorable orientation Kaempferol-3-O-rutinoside (2.9 μ M) = exception	Context-dependent	[97,137]
Lipophilicity (LogP)	↑ Optimal moderate	Balance: aqueous transport + interface partitioning PMFs (nobiletin, LogP ~3-4) optimal	LogP 2-5	[99,135]
Planarity	↑↑ Favorable	Optimal active site fit; maximizes π - π stacking Flavones > flavanones	Planar preferred	[93]

Arrow Key: ↑ = Moderate; ↑↑ = Strong; ↑↑↑ = Critical/Essential; ↓ = Decrease. **Table 2** C2=C3 double bond and C4 carbonyl essential; galloylation and dimerization dramatically enhance potency; 3-6 hydroxyl groups optimal; moderate lipophilicity (LogP 2-5) required for interface partitioning.

The SAR principles outlined in **Table 2** are exemplified by representative phytochemical structures shown in **Fig. 2**, which span three orders

of magnitude in inhibitory potency and demonstrate the critical structural features governing lipase inhibition.

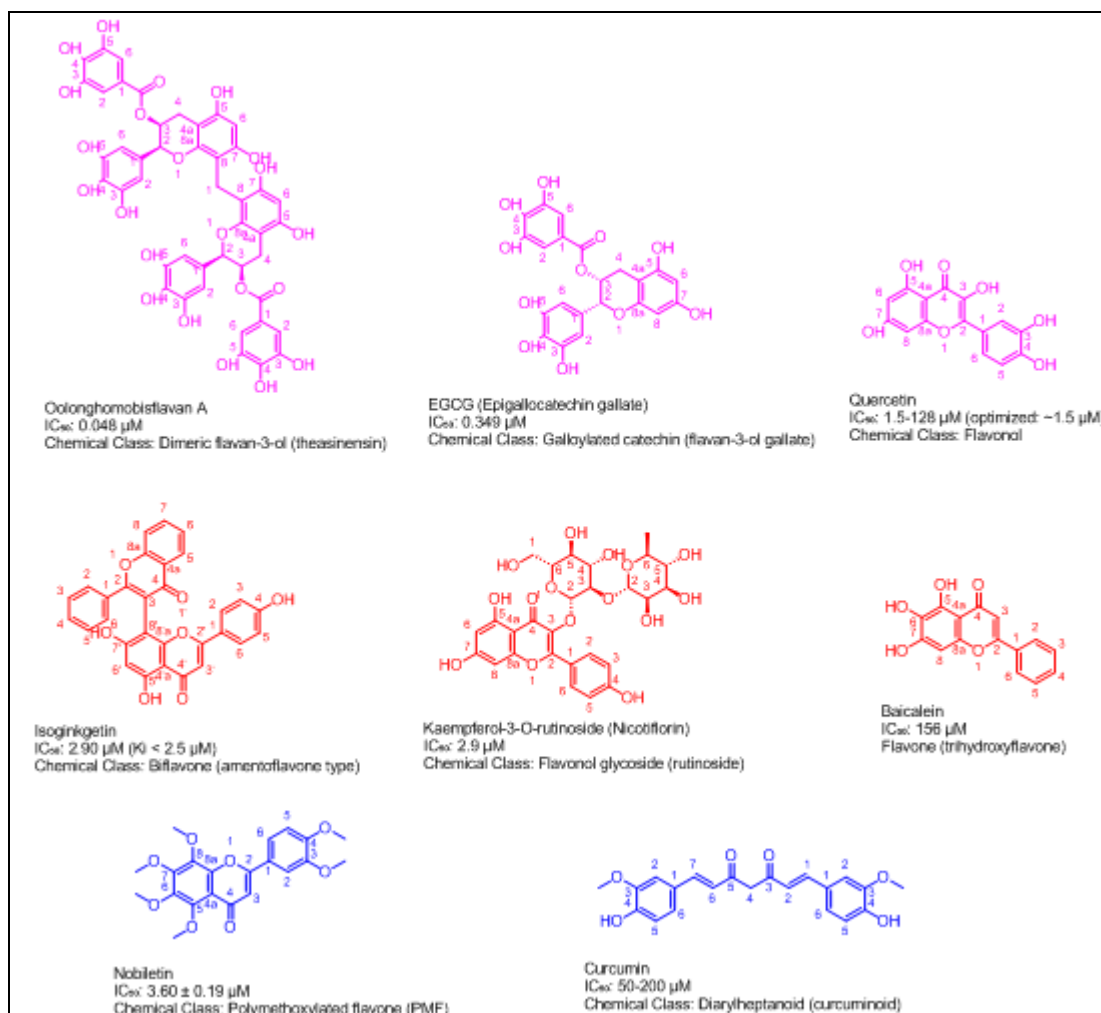


FIG. 2: REPRESENTATIVE PLANT-DERIVED PANCREATIC LIPASE INHIBITORS: CHEMICAL STRUCTURES AND REPORTED IC₅₀ VALUES

Mechanisms Beyond Lipase Inhibition and Pharmacokinetic Considerations:

Multi-Target Mechanisms: The Phytochemical Advantage: A key feature separating phytochemicals from single-target synthetic drugs is their intrinsic promiscuity the ability to modulate multiple molecular targets at once. Previously viewed as a liability under the “one drug, one target” paradigm, this polypharmacology is now recognized as beneficial for obesity, a complex multifactorial disease.

Plant-derived lipase inhibitors rarely act solely *via* pancreatic lipase; instead, they exert coordinated effects on digestive enzymes, metabolic and inflammatory pathways, and gut microbiota,

collectively engaging obesity’s intertwined pathophysiology^{141, 142}.

Dual and Multi-Enzyme Inhibition: Many phytochemical pancreatic lipase inhibitors also inhibit other digestive enzymes, particularly α -glucosidase and α -amylase, thereby reducing both dietary fat absorption and postprandial glucose excursions. This complementary activity may provide therapeutic advantages for obesity and metabolic syndrome by simultaneously targeting lipid and carbohydrate digestion.

Flavonoids such as quercetin and luteolin exhibit α -glucosidase inhibitory activity comparable to their pancreatic lipase inhibition, suggesting shared interactions with conserved enzyme active sites¹⁴³. Quinazolinone-coumarin hybrid inhibitors

demonstrated potent dual inhibition of both pancreatic lipase (IC₅₀ 2.85-3.52 μ M) and α -glucosidase, exemplifying rational design exploiting mechanistic overlap¹⁴⁴. Clinical implications remain incompletely defined. Acarbose, an FDA-approved α -glucosidase inhibitor, produces gastrointestinal side effects mechanistically analogous to orlistat's symptoms¹⁴⁵ undigested substrates reaching the colon undergo bacterial fermentation. Combining lipase and carbohydrate enzyme inhibition might exacerbate tolerability issues, necessitating careful dose optimization. Alternatively, partial inhibition of multiple targets rather than complete single-target blockade might achieve metabolic benefits with superior tolerability¹⁴².

Not all digestive enzyme inhibition is desirable; excessive tannins can impair protein digestion by inhibiting pepsin, trypsin, and chymotrypsin, compromising nutrition. Thus, selective lipase and carbohydrate-enzyme inhibition with minimal protease and micronutrient interference is essential, balancing strong efficacy with long-term nutritional safety.

Gut Microbiome Modulation: The Forgotten Organ: Emerging evidence positions the gut microbiome trillions of gastrointestinal microorganisms as critical obesity pathophysiology mediators and therapeutic targets. Polyphenols, poorly absorbed in the upper GI tract, reach the colon in substantial concentrations where resident bacteria metabolize them into diverse catabolites while polyphenols reciprocally modulate microbial community composition and metabolic activity^{146, 147}.

Tea polyphenols demonstrate prebiotic-like effects, selectively promoting beneficial bacteria including *Akkermansia muciniphila*, *Bifidobacterium*, and *Lactobacillus* species while suppressing potentially obesogenic Firmicutes. *A. muciniphila*, a mucin-degrading bacterium, inversely correlates with obesity and metabolic dysfunction; oral administration improves metabolic parameters in preclinical models and preliminary human trials.

Mechanistic connections involve multiple pathways. Beneficial bacteria produce short-chain fatty acids (SCFAs)—acetate, propionate,

butyrate—from dietary fiber and polyphenol catabolites¹⁴⁶. SCFAs exert profound effects: butyrate nourishes colonocytes with anti-inflammatory properties; propionate influences glucose homeostasis; acetate activates GPR43 receptors promoting fat oxidation. Microbial enzymes deconjugate flavonoid glycosides, generating metabolites (phenolic acids, valerolactones) with distinct bioactivities¹⁴⁷.

Inter-individual variability in microbiome composition likely contributes to heterogeneous responses to phytochemicals, with “responder” and “non-responder” phenotypes reflecting distinct baseline microbial ecologies. This framework supports future precision nutrition and phytochemical-based interventions incorporating microbiome profiling to optimize therapeutic efficacy.

Anti-Inflammatory and Antioxidant Effects: Chronic low-grade inflammation characterizes obesity, with adipose tissue macrophage infiltration, pro-inflammatory cytokine secretion (TNF- α , IL-6, IL-1 β), and oxidative stress contributing to insulin resistance and metabolic deterioration^{148–150}. Polyphenols demonstrate potent anti-inflammatory and antioxidant properties through multiple mechanisms: free radical scavenging; upregulation of endogenous antioxidant defenses (SOD, catalase, GPx) through Nrf2 activation; inhibition of pro-inflammatory signaling cascades (NF- κ B, MAPK); and modulation of inflammatory mediator production¹⁴⁶.

These effects, while not directly related to lipase inhibition, address obesity's systemic consequences and may enhance metabolic benefits. In animal models, tea polyphenols reduce inflammatory markers in adipose tissue, liver, and circulation alongside weight reduction, suggesting coordinated effects on energy balance and inflammatory tone¹⁴⁷. Evidence suggests bidirectional relationships: inflammation promotes obesity, and obesity perpetuates inflammation, creating opportunities for therapeutic intervention at multiple points⁴¹.

Adipogenesis Inhibition and Lipid Metabolism Gene Regulation: Many lipase-inhibiting phytochemicals modulate adipocyte differentiation

at molecular levels. Studies using 3T3-L1 preadipocytes the standard adipogenesis model demonstrate that flavonoids, catechins, and polyphenols suppress adipocyte differentiation, reducing lipid accumulation and expression of adipogenic transcription factors including peroxisome proliferator-activated receptor gamma (PPAR γ) and CCAAT/enhancer-binding proteins (C/EBPs)¹⁰¹.

PPAR γ , adipogenesis's master regulator, presents an intriguing paradox: thiazolidinedione drugs (pioglitazone, rosiglitazone) activate it improving insulin sensitivity despite potentially increasing adipocyte differentiation. Some polyphenols act as selective PPAR γ modulators (SPPAR γ Ms), exhibiting receptor binding with distinct conformational outcomes versus full agonists, potentially achieving insulin-sensitizing benefits without promoting adipogenesis¹⁵¹. This nuanced pharmacology exemplifies phytochemicals' capacity for subtle signaling modulation rather than binary on/off switching characteristic of synthetic drugs.

Gene expression profiling reveals polyphenols downregulate lipogenic genes (fatty acid synthase, acetyl-CoA carboxylase, stearoyl-CoA desaturase) while upregulating lipolytic and fatty acid oxidation genes (hormone-sensitive lipase, carnitine palmitoyltransferase-1, uncoupling proteins), collectively shifting adipocyte metabolism from lipid storage toward mobilization and oxidation¹⁵². These molecular effects complement reduced dietary fat absorption, creating a two-pronged attack: less fat enters the body (lipase inhibition), and existing fat stores undergo enhanced catabolism (altered gene expression)¹⁰¹.

Pharmacokinetic Considerations: The GI Localization Paradox:

Absorption Challenges as Therapeutic Advantages: Conventional drug development prioritizes oral bioavailability for systemic distribution. For pancreatic lipase inhibitors, this paradigm inverts: the target enzyme resides in the intestinal lumen, making systemic absorption unnecessary and potentially undesirable. Orlistat exemplifies this: extremely lipophilic (LogP 8.9), it exhibits negligible systemic absorption (<1%), with

>95% excreted unchanged in feces². This GI localization contributes to orlistat's favorable safety profile despite chemical reactivity.

Many polyphenolic lipase inhibitors face "poor bioavailability" a characterization assuming systemic distribution as the goal. For lipase inhibition specifically, poor absorption represents an asset: high concentrations persist in the intestinal lumen throughout the postprandial period when lipase activity peaks, maximizing enzyme inhibition while minimizing systemic exposure. EGCG, for instance, shows poor absorption (oral bioavailability 0.1-1.7%) yet achieves substantial lipase inhibition *in-vivo*^{45, 147}.

Unlike typical drugs, lipase inhibitor formulations prioritize GI retention, mucosal contact, and degradation resistance over absorption sustaining duodenal/jejunal concentrations at the action site

Metabolic Transformations: Friend or Foe?:

Polyphenols undergo extensive metabolism: Phase I oxidation/reduction by cytochrome P450 enzymes; Phase II conjugation (glucuronidation, sulfation, methylation); and gut microbiota biotransformation (deglycosylation, ring fission, dehydroxylation)¹⁴⁷. These transformations profoundly alter chemical structures and bioactivities. For GI-localized lipase inhibitors, metabolism relationships differ fundamentally. Parent compounds (flavonoid glycosides, polymeric catechins) may undergo deglycosylation by intestinal β -glucosidases or bacterial enzymes, releasing more active aglycones with superior lipase inhibitory potency¹⁵³. Conversely, Phase II conjugation could inactivate absorbed compounds before systemic circulation—beneficial for safety, inconsequential for efficacy if inhibition occurs luminally¹⁴⁷.

Gut microbiota transformations create complex scenarios. Bacterial C-ring fission produces phenolic acids with distinct activities. Current evidence suggests some catabolites retain modest lipase inhibitory activity, while others demonstrate complementary bioactivities (anti-inflammatory, antioxidant)¹⁴⁷.

Temporal dynamics matter critically. Lipase inhibitors must act during the 2-4 hour postprandial window. Compounds requiring extensive microbial

transformation (6+ hours post-ingestion) miss direct lipase inhibition windows, though metabolites may exert delayed metabolic effects. Immediate-acting parent compounds versus delayed-acting metabolites create biphasic activity profiles potentially extending therapeutic windows.

Food Matrix Effects and Bioaccessibility: Unlike pharmaceutical dosage forms that deliver isolated active compounds, dietary phytochemicals are consumed within complex food matrices that influence their bioaccessibility and luminal activity¹⁵⁴. Tea polyphenols, consumed as aqueous infusions, exhibit high immediate bioaccessibility because they are already solubilized and can rapidly interact with intestinal contents and pancreatic lipase¹⁵⁵. In contrast, polyphenols present in whole fruits and vegetables are frequently bound within cellular structures and require mechanical processing and enzymatic digestion for release¹⁵⁶. Food processing techniques such as chopping, blending, cooking, and fermentation markedly alter polyphenol release kinetics and intestinal availability¹⁵⁷.

Dietary lipids may enhance inhibitory efficacy by promoting polyphenol partitioning at the lipid–water interface where pancreatic lipase functions, thereby increasing local inhibitor concentrations¹⁵⁸. Conversely, polyphenol–protein interactions, particularly those involving tannins, can reduce inhibitor availability and impair protein digestion¹⁵⁹.

Advanced delivery systems, including microencapsulation, nanoparticles, phytosomes, and liposomes, improve phytochemical stability, targeted intestinal release, and localization at the lipid–water interface, thereby enhancing pancreatic lipase inhibitory efficacy.

Inter-Individual Variability: Genetics, Microbiome, and Phenotypes: Clinical trials consistently demonstrate large inter-individual variability in botanical supplement responses. This heterogeneity reflects multiple factors: genetic polymorphisms affecting metabolizing enzymes (CYP450s, UGTs, SULTs, COMT) alter polyphenol metabolism rates; baseline gut microbiome composition determines biotransformation capacity; physiological factors

including gastric pH, intestinal transit time, and bile salt secretion influence polyphenol stability^{160, 161}.

The concept of "metabotypes"—distinct metabolic phenotypes producing characteristic polyphenol metabolite profiles has emerged from metabolomics studies. Individuals cluster into groups based on urinary metabolite patterns, with clustering driven primarily by gut microbiota composition. For lipase inhibitors, metabotype differences might predict therapeutic responses¹⁶².

Microbiome profiling, genetic testing for enzyme polymorphisms, and adaptive biomarker dosing enable personalized polyphenol therapy. Precision nutrition requires prospective trials and affordable tools for clinical practicality¹⁶³.

The Desirable Low-Absorption Profile: Safety Implications: The limited systemic absorption of many polyphenolic pancreatic lipase inhibitors contributes to their favorable safety profile by restricting activity primarily to the gastrointestinal tract, thereby minimizing systemic adverse effects, drug–drug interactions, and off-target toxicity^{45, 147}. Consequently, most phytochemicals do not achieve plasma concentrations sufficient to produce clinically significant systemic effects following oral administration.

Clinical studies generally report a low incidence of serious adverse events, with gastrointestinal symptoms such as nausea, diarrhea, and abdominal discomfort representing the most common treatment-related effects¹⁰⁷.

Rare hepatotoxicity reports associated with concentrated green tea extracts appear dose-dependent, likely reflecting exceptionally high catechin absorption overwhelming hepatic detoxification or individual susceptibility¹⁶⁴.

The safety-efficacy balance differs fundamentally from orlistat: both produce GI side effects from unabsorbed fat, but phytochemicals generally exhibit milder symptoms at efficacious doses, presumably reflecting lower potency (IC₅₀ values 10-1000× higher than orlistat) requiring less complete lipase inhibition¹⁶⁵. This moderate inhibition may provide a favorable balance between therapeutic efficacy and tolerability by reducing

dietary fat absorption without inducing severe malabsorption.

Clinical Translation, Challenges, and Future Directions

From Bench to Bedside: The Translation Gap:

Although numerous phytochemicals exhibit potent pancreatic lipase inhibition in vitro and promising preclinical efficacy, clinical evidence remains limited. Major barriers to translation include differences between experimental and physiological gastrointestinal conditions, variable bioavailability, inconsistent botanical standardization, and the scarcity of well-designed randomized controlled trials ⁴⁵.

Green tea catechins represent the most clinically-studied phytochemical lipase inhibitors. Meta-analyses demonstrate modest but consistent weight loss (approximately 1-2 kg greater than placebo over 12 weeks), with improvements in waist circumference and metabolic parameters. However, disentangling lipase inhibition from catechins' other mechanisms—thermogenesis enhancement, fat oxidation promotion, appetite modulation—remains challenging ¹⁶⁶. Studies measuring fecal fat excretion show increases confirming reduced fat absorption, though magnitudes (10-15% increases) lag behind orlistat's effects (30% reduction).

Traditional herbal formulations from TCM and Ayurveda demonstrate clinical benefits in trials conducted primarily in Asian countries, though methodological limitations preclude definitive conclusions. The challenge involves balancing respect for traditional practice with scientific demands for standardization and controlled comparisons.

Formulation Innovations: Enhancing Delivery and Tolerability:

Advanced drug delivery technologies offer opportunities to optimize phytochemical lipase inhibitor performance. Nanoparticle formulations enhance polyphenol stability, enable controlled release, ¹⁶⁷ and improve mucosal adhesion, potentially increasing local GI concentrations during critical postprandial periods. Enteric coating technologies enable pH-dependent release, protecting acid-labile polyphenols through gastric transit while releasing contents in the duodenum where lipase activity peaks ¹⁶⁸.

Combination strategies merit exploration: co-formulating complementary inhibitors might achieve synergistic effects; pairing with prebiotics/probiotics could enhance microbiome benefits; adding fat-soluble vitamin supplementation could prevent deficiencies from chronic fat malabsorption.

Regulatory Pathways and Market Positioning:

Botanical lipase inhibitors face complex regulatory landscapes varying internationally. In the United States, the dietary supplement framework permits marketing without FDA pre-approval, enabling rapid market entry but limiting promotional messaging ¹⁶⁹. Europe's traditional herbal medicinal products directive provides an intermediate pathway recognizing long-standing traditional use ¹⁷⁰. Asian markets maintain robust frameworks for traditional medicine products.

Market positioning proves critical. Competing directly with pharmaceutical obesity medications proves challenging given modest efficacy ¹⁷¹. Instead, positioning as preventive nutritional supplements, functional food ingredients, or adjunct therapies exploits phytochemicals' strengths—safety, naturalness, cultural acceptance, multi-target benefits ¹⁷².

Future Research Priorities and Emerging Opportunities:

Untapped Botanical Resources: The majority of Earth's 400,000+ plant species remain chemically uncharacterized. Biodiversity hotspots, marine sources, and extremophile plants offer structurally-distinct compounds with potentially novel mechanisms ¹⁴⁷.

Biotechnological Production: Plant cell culture, metabolic engineering, and synthetic biology enable sustainable production ¹⁷³. CRISPR-based genome editing could enhance biosynthetic pathway flux ¹⁷⁴. Heterologous expression in microbial hosts could produce complex plant natural products through fermentation.

Artificial Intelligence: Machine learning algorithms can predict lipase inhibitory potential from chemical structures, enabling virtual screening. Natural product databases provide training data for predictive models ¹⁷⁵.

Personalized Nutrition: Integration of genomics, metabolomics, and microbiomics promises individualized botanical interventions¹⁷⁶. Microbiome profiling, genetic testing, and metabolomic phenotyping would guide selection of optimal phytochemical inhibitors and dosing regimens¹⁷⁷.

CONCLUSIONS: The global obesity crisis demands strategies that extend beyond conventional pharmacotherapy. Phytochemical pancreatic lipase inhibitors, rooted in traditional medical systems and increasingly supported by mechanistic research, offer complementary advantages: multi-target activity matching obesity's complex pathophysiology, predominantly gastrointestinal action with favorable safety, cultural acceptability, and potential cost-effectiveness, especially in preventive and resource-limited settings. This review surveys polyphenols, terpenoids, alkaloids, and bioactive peptides, emphasizing structure–activity features such as hydroxylation patterns, aromatic planarity, and galloylation. Evidence now supports traditional anti-obesity botanicals showing lipase inhibition, metabolic and anti-inflammatory effects, and microbiome modulation.

Despite modest potency versus GLP-1 agonists, limited clinical data, and standardization issues, these agents fit roles in preventive nutrition, adjunctive therapy, and mild obesity management, guided by ethnopharmacology, modern analytics, innovative formulations, and sustainable sourcing.

ACKNOWLEDGEMENT: The authors gratefully acknowledge the Almighty for guidance and strength, their families for unwavering support and, and Sumandeep Vidyapeeth deemed to be University, Waghodia, for providing the necessary institutional support and facilities that enabled the successful completion of this work.

AI Disclosure: Artificial intelligence tools (ChatGPT, GPT-5, OpenAI, USA) were used only for language refinement and grammar correction. All scientific content and interpretations are solely those of the authors.

Author Contributions: The authors of this paper have adhered to the guidelines of the International Committee of Medical Journal Editors (ICMJE),

contributed significantly to the study, and approved the final manuscript for submission and publication.

Financial Support: The author has independently prepared this paper for publication based on their own research and efforts.

Ethical Approvals: As this study did not involve animals or humans, no ethical clearance was required.

Data Availability: All data generated and analysed for this study have been included in the research article.

CONFLICTS OF INTEREST: Our research and findings are driven solely by scientific merit and integrity, without any competing interests.

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<https://pmc.ncbi.nlm.nih.gov/articles/PMC5484307/>

How to cite this article:

Panchal NB and Vaghela VM: "Plant-derived pancreatic lipase inhibitors: ethnopharmacology, phytochemistry, and therapeutic potential in obesity". *Int J Pharm Sci & Res* 2026; 17(11): 3267-91. doi: 10.13040/IJPSR.0975-8232.17(11).3267-91.

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