Plant-Derived Compounds for Anti-obesity Therapeutics

Liam Alexander Dubois [1*], Emma Charlotte Carter [2], Noah Benjamin McKenzie [3]
[1] Department of Pharmaceutical Sciences, University of Toronto, Canada
[2] Faculty of Pharmacy, Université de Montréal, Canada
[3] Institute for Biomaterials and Biomedical Engineering, UBC, Canada

* Corresponding Author: **Liam Alexander Dubois**

Article Info

ISSN (online): 3107-393X
Volume: 02
Issue: 03
May-June 2025
Received: 17-03-2025
Accepted: 20-04-2025
Published: 16-05-2025
Page No: 33-39

Abstract
Obesity represents one of the most pressing public health challenges of the twenty-first century, affecting more than 650 million adults globally and contributing substantially to the burden of cardiovascular disease, type 2 diabetes mellitus, musculoskeletal disorders, and several malignancies. Current pharmacological interventions, including orlistat, naltrexone-bupropion, and glucagon-like peptide-1 receptor agonists, provide meaningful weight reduction in select populations; however, their clinical utility is frequently constrained by significant adverse effect profiles, high cost, and limited long-term tolerability. There is consequently a pressing need for the identification and development of safer, more accessible, and mechanistically diverse anti-obesity agents. Plant-derived compounds—encompassing polyphenols, flavonoids, alkaloids, terpenoids, dietary fibers, and saponins—have garnered considerable scientific interest as candidate therapeutics, owing to their structural diversity and multifaceted pharmacological properties. These phytochemicals exert anti-obesity effects through several converging mechanisms, including the inhibition of pancreatic lipase activity, suppression of adipogenesis via peroxisome proliferator-activated receptor gamma downregulation, activation of AMP-activated protein kinase, enhancement of thermogenesis through uncoupling protein-1 induction, appetite modulation via incretin and leptin signaling pathways, and prebiotic modulation of intestinal microbiota composition. Preclinical evidence from both *in vitro* and rodent models is substantial; however, the translational path to clinical application remains challenged by poor bioavailability, lack of standardization, and limited Phase II and III trial data. This review critically examines the mechanistic basis, preclinical landscape, clinical evidence, and formulation strategies for plant-derived anti-obesity compounds, and provides a synthesis of future directions for their development as evidence-based therapeutics.

Keywords: Plant-derived compounds, Obesity, Anti-obesity therapeutics, Phytochemicals, Metabolic regulation, Translational research

1. Introduction

Obesity is a chronic, multifactorial metabolic disorder defined by the World Health Organization as a body mass index equal to or exceeding 30 kg/m², and is now recognized as a global epidemic of unprecedented proportions [1]. The prevalence of obesity has nearly tripled since 1975, with current estimates placing the number of affected adults worldwide at over 650 million, and projections suggesting this figure will surpass one billion by 2030 [2]. The clinical consequences of obesity are extensive and include type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease, polycystic ovarian syndrome, and increased risk of several cancers, collectively imposing a staggering socioeconomic burden estimated at trillions of United States dollars annually [3].

Current therapeutic strategies for obesity management include lifestyle modification, pharmacotherapy, and bariatric surgery. While lifestyle interventions remain the cornerstone of treatment, achieving and maintaining clinically significant weight loss—typically defined as five percent or more of initial body weight—is difficult for the majority of patients without adjunctive pharmacological support [4]. Approved pharmacotherapies such as orlistat, naltrexone-bupropion, phentermine-topiramate, and semaglutide offer varying degrees of efficacy; however, each is associated with notable limitations. Orlistat causes gastrointestinal adverse effects including steatorrhea and fecal urgency [5]. Naltrexone-bupropion is contraindicated in patients with seizure disorders and carries neuropsychiatric warnings [6]. Semaglutide, while effective, requires subcutaneous injection and is prohibitively expensive for many healthcare systems [7]. These constraints underscore the urgent need for the discovery of novel, safe, and cost-effective pharmacological agents.

Plant-derived compounds have historically underpinned a substantial proportion of pharmacological development; it is estimated that more than fifty percent of approved drugs are derived from or inspired by natural product scaffolds [8]. Phytochemicals—the biologically active secondary metabolites of plants—represent a structurally diverse chemical space with demonstrated anti-obesity activity across multiple preclinical and, increasingly, clinical study paradigms [9]. Their mechanisms of action are heterogeneous and frequently synergistic, targeting adipogenesis, energy expenditure, lipid metabolism, and intestinal microbial ecology simultaneously [10]. This review provides a comprehensive and critically reasoned analysis of plant-derived compounds as anti-obesity therapeutics, with particular emphasis on mechanistic pathways, preclinical-to-clinical translation, formulation innovation, and regulatory considerations.

2. Pathophysiology of Obesity

The pathophysiology of obesity involves a complex interplay of genetic predisposition, environmental exposures, and dysregulated neuroendocrine and metabolic signaling. At its core, obesity results from a sustained positive energy balance in which caloric intake chronically exceeds energy expenditure, leading to progressive accumulation of adipose tissue [11]. Adipogenesis—the differentiation of preadipocytes into mature lipid-laden adipocytes—is orchestrated by a network of transcription factors, most notably peroxisome proliferator-activated receptor gamma (PPAR-γ) and the CCAAT/enhancer-binding proteins (C/EBPs), which drive the expression of lipogenic enzymes including fatty acid synthase and acetyl-CoA carboxylase [12].

Hypothalamic regulation of appetite and energy homeostasis plays a critical role in the genesis and perpetuation of obesity. The arcuate nucleus integrates peripheral hormonal signals, including leptin from adipose tissue, ghrelin from the gastric fundus, peptide YY and glucagon-like peptide-1 from the intestinal L-cells, and insulin from the pancreatic beta cells, to modulate food intake via orexigenic and anorexigenic neuronal circuits [13]. In obesity, leptin resistance—characterized by the failure of elevated circulating leptin to suppress appetite—is a central neuroendocrine aberration that perpetuates hyperphagia and weight gain [14].

At the cellular level, obesity-associated adipose tissue expansion leads to adipocyte hypertrophy, dysregulated adipokine secretion, and macrophage infiltration, culminating in a state of chronic low-grade inflammation characterized by elevated circulating levels of tumor necrosis factor-alpha, interleukin-6, and C-reactive protein [15]. This inflammatory milieu contributes to peripheral insulin resistance, hepatic steatosis, and pancreatic beta-cell dysfunction, creating a vicious cycle of metabolic derangement. Simultaneously, impaired mitochondrial biogenesis and reduced brown adipose tissue thermogenic activity—mediated by decreased uncoupling protein-1 (UCP-1) expression—contribute to diminished energy expenditure and the accumulation of ectopic lipid deposits [16].

3. Major Classes of Plant-Derived Compounds

Plant-derived compounds with anti-obesity potential are classified into several broad categories based on their chemical structure and biosynthetic origin. Polyphenols constitute the most extensively studied class and include stilbenes, curcuminoids, lignans, and phenolic acids. Resveratrol, a stilbene found abundantly in grape skin and red wine, and epigallocatechin-3-gallate (EGCG), the principal catechin of green tea, have been particularly well characterized for their metabolic regulatory properties [17]. Curcumin, the principal polyphenolic constituent of Curcuma longa, exerts pleiotropic anti-inflammatory and anti-adipogenic effects and has been the subject of numerous clinical investigations [18].

Flavonoids represent another structurally diverse class encompassing flavonols, flavanones, flavones, isoflavones, and anthocyanins. Quercetin, naringenin, and kaempferol have demonstrated inhibitory activity against pancreatic lipase and modulatory effects on adipokine secretion [19]. Alkaloids, including berberine from Berberis species, capsaicin from Capsicum annuum, and caffeine from Coffea arabica, are notable for their thermogenic and energy expenditure-enhancing properties [20]. Terpenoids—comprising monoterpenes, diterpenes, and triterpenes—include ursolic acid and oleanolic acid, which have shown promising anti-adipogenic activity in rodent models [21].

Dietary fibers, including soluble fibers such as pectin, beta-glucan, and inulin, contribute to satiety by delaying gastric emptying and attenuating postprandial glycemic excursions, while simultaneously acting as prebiotics to favorably modulate gut microbiota composition [22]. Saponins, such as the ginsenosides from Panax ginseng and soyasaponins from Glycine max, have demonstrated inhibitory effects on intestinal cholesterol absorption and adipocyte lipid accumulation [23]. Conjugated linoleic acid (CLA), derived from dairy products and certain plant oils, has been shown in meta-analyses to reduce body fat mass modestly but consistently when supplemented over extended periods [24].

4. Mechanisms of Anti-Obesity Action

The anti-obesity mechanisms of plant-derived compounds are diverse and frequently synergistic, targeting multiple nodes of metabolic regulation simultaneously. Inhibition of pancreatic lipase represents one of the most clinically validated mechanisms; quercetin, EGCG, and several flavonoids competitively inhibit this enzyme, thereby reducing the hydrolysis and subsequent absorption of dietary triglycerides and producing an effect mechanistically analogous to orlistat [25]. Unlike orlistat, however, plant-derived lipase inhibitors tend to produce this effect at

concentrations that are achievable without the gastrointestinal adverse effects associated with the pharmaceutical agent.

Activation of AMP-activated protein kinase (AMPK) is a central mechanism through which several phytochemicals—most notably berberine, resveratrol, and EGCG—exert their metabolic effects. AMPK serves as a cellular energy sensor that, upon activation, suppresses anabolic pathways including de novo lipogenesis and cholesterol synthesis, while simultaneously promoting fatty acid oxidation and mitochondrial biogenesis [26]. Berberine has been demonstrated in multiple preclinical and clinical studies to activate AMPK with potency comparable to that of metformin, reducing hepatic lipid accumulation and improving insulin sensitivity [27].

Enhancement of thermogenesis represents a mechanistically appealing anti-obesity strategy, as increasing resting energy expenditure even modestly can produce meaningful reductions in adiposity over time. Capsaicin and its non-pungent analogue capsinoids activate transient receptor potential vanilloid-1 (TRPV1) channels, triggering sympathetic nervous system-mediated thermogenesis and increasing UCP-1 expression in brown adipose tissue [28]. Similarly, EGCG has been shown to potentiate norepinephrine signaling by inhibiting catechol-O-methyltransferase, thereby prolonging adrenergic stimulation of thermogenic pathways [17].

Appetite regulation is another important axis of anti-obesity action. Several plant-derived compounds modulate the secretion of satiety hormones including glucagon-like peptide-1 (GLP-1), cholecystokinin, and peptide YY from enteroendocrine cells, thereby promoting a sustained sensation of fullness and reducing caloric intake [29]. Dietary fibers exert particularly well-characterized effects on appetite through the stimulation of GLP-1 and peptide YY release, acting through fermentation-derived short-chain fatty acids that bind to G-protein coupled receptors GPR41 and GPR43 on intestinal L-cells [22].

The gut microbiome has emerged as a critical mediator of metabolic homeostasis, and its modulation by plant-derived compounds represents an increasingly recognized anti-obesity mechanism. Phytochemicals including quercetin, resveratrol, and dietary fibers selectively promote the growth of beneficial bacterial taxa such as Lactobacillus and Bifidobacterium, while suppressing the expansion of Firmicutes relative to Bacteroidetes—a microbial ratio shift associated with obesity and increased energy harvest from dietary substrates [30].

5. Preclinical and Translational Research

The preclinical evidence base for plant-derived anti-obesity compounds is extensive. *in vitro* studies using 3T3-L1 preadipocyte cell lines and primary adipocyte cultures have provided mechanistic insights into the anti-adipogenic properties of compounds such as curcumin, EGCG, and ursolic acid, demonstrating dose-dependent suppression of PPAR-γ expression, inhibition of lipid droplet accumulation, and attenuation of inflammatory cytokine secretion [31]. These findings have been corroborated in rodent models of diet-induced obesity and genetic obesity, in which oral administration of various phytochemicals has produced significant reductions in body weight, adipose tissue mass, serum lipid profiles, and hepatic steatosis [32].

However, the translational relevance of preclinical data is frequently undermined by critical pharmacokinetic challenges. Many plant-derived compounds exhibit poor oral bioavailability owing to limited aqueous solubility, rapid first-pass hepatic metabolism, and extensive intestinal conjugation. Curcumin, for example, demonstrates extremely low systemic bioavailability following oral administration in its native form, necessitating formulation strategies to achieve therapeutically relevant plasma concentrations [33]. Similarly, resveratrol undergoes rapid sulfation and glucuronidation, resulting in short plasma half-life and low free compound exposure despite substantial *in vitro* potency [34].

Animal models of obesity, while valuable for mechanistic exploration, frequently employ supraphysiological doses or administration routes not applicable to human subjects, further complicating direct translation. The majority of preclinical studies use high-fat diet-induced obesity in mice, which does not fully replicate the neuroendocrine, behavioral, and genetic complexity of human obesity. Standardization of animal models, dose selection rationale, and pharmacokinetic profiling are essential preconditions for meaningful clinical trial design [35].

6. Clinical Evidence

Clinical evidence for plant-derived anti-obesity compounds is accumulating, though it remains considerably less robust than the preclinical literature. Randomized controlled trials of berberine have reported reductions in body mass index, fasting glucose, total cholesterol, and triglycerides, with effect magnitudes comparable to those of metformin and statins in selected metabolic outcomes [27]. EGCG supplementation has been associated with modest but statistically significant reductions in body weight and waist circumference in meta-analyses of randomized trials, with the greatest effects observed in Asian populations and at doses exceeding 300 milligrams per day [17].

Curcumin has demonstrated anti-inflammatory and lipid-lowering effects in clinical trials, although its impact on body weight per se is less consistently demonstrated, likely owing to the bioavailability limitations described above [18]. Clinical trials of dietary fibers—particularly beta-glucan and inulin—have consistently reported improvements in satiety, postprandial glycemia, and lipid profiles, with some studies demonstrating modest weight loss over twelve to twenty-four weeks of supplementation [22].

Significant limitations constrain the clinical evidence base. Study heterogeneity in terms of compound source, dose, formulation, duration, and patient population makes meta-analytic synthesis challenging. Many trials are underpowered, of short duration, and fail to employ standardized outcome measures. The natural variability of plant-derived preparations—influenced by agricultural practices, geographic origin, and extraction methodology—introduces confounding that reduces reproducibility across research groups [36]. Placebo-controlled designs are further complicated by the organoleptic properties of many phytochemical preparations, which can compromise blinding. Robust, large-scale, multi-center Phase III trials employing pharmaceutical-grade standardized preparations are urgently needed.

7. Formulation Strategies and Emerging Delivery Systems

Addressing the bioavailability limitations of plant-derived anti-obesity compounds has become a central focus of pharmaceutical development. Nanoparticle-based delivery systems—including polymeric nanoparticles, solid lipid nanoparticles, and self-nanoemulsifying drug delivery systems—have demonstrated considerable promise in augmenting the systemic bioavailability of poorly soluble phytochemicals [37]. Curcumin encapsulated in poly(lactic-co-glycolic acid) nanoparticles has achieved plasma concentrations several-fold higher than those attainable with native curcumin, while exhibiting superior stability and sustained release kinetics [33].

Phospholipid complexation represents another validated strategy for enhancing the oral bioavailability of phenolic compounds. Phytosome technology, which involves the formation of a complex between a plant extract and phosphatidylcholine, has been applied to EGCG, resveratrol, and curcumin, yielding formulations with markedly improved intestinal absorption and reduced first-pass metabolism [38]. Cyclodextrin inclusion complexes have similarly been employed to enhance aqueous solubility and mucosal permeability.

Lipid-based drug delivery systems, including nanoemulsions and self-microemulsifying formulations, are particularly well-suited for lipophilic terpenoids and polyphenols, providing a hydrophilic vehicle that facilitates intestinal lymphatic transport and circumvents hepatic first-pass extraction. Emerging approaches include exosome-mimetic nanocarriers derived from edible plant materials—such as ginger and grape—which offer inherent biocompatibility, immunological tolerance, and natural targeting capabilities that synthetic polymers cannot replicate [37]. Microencapsulation of dietary fibers and probiotic-phytochemical co-formulations represent additional innovation frontiers aimed at optimizing gastrointestinal stability and targeted delivery to the distal intestine.

8. Regulatory, Safety, and Commercialization Challenges

The development of plant-derived compounds as approved anti-obesity pharmaceuticals faces a complex regulatory landscape. In most jurisdictions, phytochemical preparations are classified as dietary supplements rather than drugs, a designation that both facilitates market entry and simultaneously restricts the permissible scope of efficacy claims and the mandatory rigor of clinical evidence [39]. Transitioning from supplement to pharmaceutical drug status requires the generation of robust Phase II and Phase III clinical trial data demonstrating defined clinical endpoints—such as a minimum five percent weight loss relative to placebo—along with a well-characterized safety and tolerability profile.

Safety considerations are multifaceted. Although many plant-derived compounds have centuries-long histories of traditional use, formal pharmacovigilance data are frequently incomplete or absent. Clinically significant herb-drug interactions have been documented for several widely consumed phytochemicals; St. John's Wort, for example, is a potent inducer of cytochrome P450 3A4 and P-glycoprotein, reducing plasma concentrations of numerous co-administered medications [40]. Berberine inhibits multiple CYP isoforms and may potentiate the hypoglycemic effects of antidiabetic agents. Systematic assessment of the interaction potential of candidate compounds using standardized *in vitro* and clinical pharmacokinetic methodologies is therefore essential prior to broader therapeutic application.

Commercialization of plant-derived anti-obesity agents is further complicated by challenges in sourcing consistency, intellectual property protection, and the economics of clinical development. Natural products present inherent difficulties in patent protection relative to synthetic small molecules, as they are typically not novel chemical entities, although formulations, extraction processes, and defined compositions may be patentable. Geographic and seasonal variability in phytochemical content necessitates the implementation of rigorous good manufacturing practice standards and batch-specific phytochemical fingerprinting to ensure therapeutic-grade consistency and regulatory compliance [36].

9. Conclusion and Future Directions

Plant-derived compounds occupy a scientifically compelling and clinically promising position in the therapeutic landscape for obesity management. Their structural diversity, mechanistic breadth, and established safety profiles in traditional medicinal contexts provide a strong foundation for translational development. Key mechanisms—including AMPK activation, PPAR-γ suppression, thermogenesis induction, incretin-mediated appetite regulation, and gut microbiota modulation—collectively position phytochemicals as multimodal anti-obesity agents capable of addressing the complex pathophysiology of this condition in ways that single-target synthetic drugs cannot.

The principal barriers to translational success lie in the domains of bioavailability, standardization, and clinical evidence generation. Advanced delivery systems, including nanoparticle encapsulation, phytosome technology, and plant-derived nanocarriers, offer credible solutions to pharmacokinetic limitations and should be prioritized in formulation development pipelines. Concurrently, the conduct of well-designed, adequately powered, Phase III randomized controlled trials employing standardized, pharmaceutical-grade phytochemical preparations is essential to establish the clinical evidence base required for regulatory approval and integration into evidence-based clinical guidelines.

Future research directions should include the application of network pharmacology and systems biology approaches to elucidate synergistic interactions among phytochemical combinations, the use of pharmacogenomic profiling to identify patient subpopulations most likely to benefit from specific plant-derived agents, and the development of phytochemical-synthetic hybrid molecules that combine the multi-target activity of natural products with the pharmacokinetic tractability of small molecule drugs. The convergence of precision medicine, microbiome science, and advanced pharmaceutical technology creates an unprecedented opportunity to elevate plant-derived compounds from traditional remedies to rigorously validated, accessible, and effective components of modern anti-obesity pharmacotherapy.

Figures

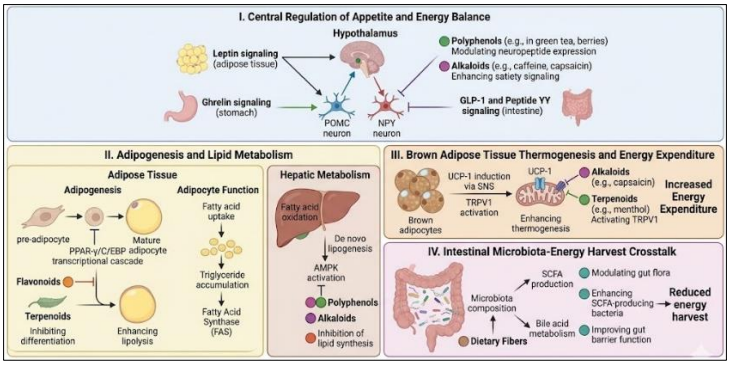

Fig 1: Key metabolic pathways involved in obesity and the mechanistic intervention points of plant-derived compounds.

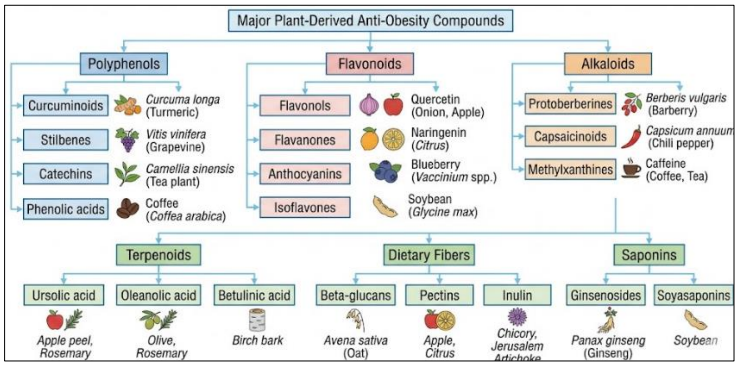

Fig 2: Classification and botanical sources of major plant-derived anti-obesity compounds.

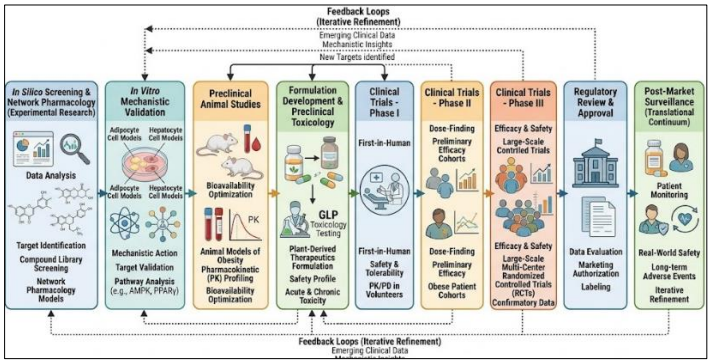

Fig 3: Translational pathway from experimental research to clinical application in plant-derived anti-obesity therapeutics.

Tables

Table 1: Comparison of Major Plant-Derived Compound Classes, Botanical Sources, and Mechanisms of Anti-Obesity Action

Compound Class	Representative Agents	Primary Sources	Mechanisms of Anti-Obesity Action
Polyphenols	Resveratrol, EGCG, Curcumin	Grapes, green tea, turmeric	AMPK activation, PPAR-γ downregulation, suppression of lipogenesis, anti-inflammatory activity
Flavonoids	Quercetin, Naringenin, Kaempferol	Citrus fruits, onions, berries	Inhibition of pancreatic lipase, modulation of adipokines, appetite suppression via GLP-1 enhancement
Alkaloids	Berberine, Caffeine, Capsaicin	Berberis spp., coffee, chili pepper	AMPK-mediated glucose uptake, thermogenesis via UCP-1, SNS activation, inhibition of adipocyte differentiation
Terpenoids	Ursolic acid, Oleanolic acid, Betulinic acid	Rosemary, olive, birch bark	Inhibition of α-glucosidase, reduction of triglyceride accumulation, modulation of insulin signaling
Dietary Fibers	Pectin, Beta-glucan, Inulin	Oats, apples, chicory root	Delayed gastric emptying, attenuation of postprandial glucose spikes, prebiotic modulation of gut microbiota
Saponins	Ginsenosides, Soyasaponins	Panax ginseng, soybeans	Inhibition of cholesterol absorption, suppression of lipid accumulation, anti-adipogenic signaling
Essential Fatty Acids	Conjugated linoleic acid (CLA)	Dairy, safflower oil	Reduction of body fat mass, enhancement of fatty acid oxidation, modulation of PPARα

AMPK, AMP-activated protein kinase; PPAR-γ, peroxisome proliferator-activated receptor gamma; GLP-1, glucagon-like peptide-1; UCP-1, uncoupling protein-1; SNS, sympathetic nervous system; PPARα, peroxisome proliferator-activated receptor alpha.

Table 2: Advantages, Limitations, and Clinical Considerations of Plant-Based Anti-Obesity Therapies

Parameter	Advantages	Limitations	Clinical Considerations
Safety Profile	Generally well tolerated; lower risk of systemic adverse effects compared to synthetic agents	Potential herb-drug interactions; lack of standardization across preparations	Long-term safety data remain limited; adverse effects may be dose-dependent
Efficacy	Multimodal mechanisms targeting several obesity pathways simultaneously	Modest effect sizes in clinical trials; highly variable inter-individual response	Combination with lifestyle intervention may enhance efficacy
Bioavailability	Some compounds (e.g., EGCG, berberine) demonstrate favorable intestinal uptake	Poor oral bioavailability for many phytochemicals due to rapid metabolism and low solubility	Nanoformulation and lipid-based carriers may significantly improve systemic exposure
Regulatory Status	Many compounds available as dietary supplements with existing safety data	Not classified as pharmaceuticals in most jurisdictions; efficacy claims are restricted	Pathway to drug approval requires rigorous phase II/III clinical evidence
Standardization	Advances in quality control and phytochemical fingerprinting improving batch consistency	Natural product variability due to geographic, seasonal, and processing factors	GMP compliance and certificate of analysis essential for therapeutic-grade products
Cost and Access	Relatively low cost of raw plant material; broad geographic availability	Processing, purification, and delivery system development increase costs substantially	Cost-effectiveness analyses needed to justify clinical integration

GMP, good manufacturing practice.

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