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Review

Piceatannol as a Multitarget Modulator of Obesity-Associated Metabolic Dysfunction: From Molecular Mechanisms to Clinical Translation

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Abstract

Background/Objectives: Obesity is a multifactorial chronic disease involving adipose tissue dysfunction, low-grade inflammation, oxidative stress, mitochondrial dysfunction, and insulin resistance, contributing to type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease, cardiovascular disease, and other complications. Piceatannol (3,3′,4,5′-tetrahydroxystilbene), a naturally occurring stilbene related to resveratrol, has attracted interest for its potential to modulate these interconnected processes. This narrative review critically synthesizes mechanistic, pharmacokinetic, preclinical, clinical, and translational evidence concerning piceatannol in adipose tissue dysfunction, metabolic inflammation, and insulin resistance and identifies major knowledge gaps and research priorities. Methods: PubMed/MEDLINE, Scopus, Web of Science Core Collection, and Google Scholar were searched from inception through 31 August 2026 for in vitro, animal, and human studies examining piceatannol in obesity, adipose tissue biology, inflammation, oxidative stress, glucose and lipid metabolism, insulin resistance, pharmacokinetics, and bioavailability. Evidence was synthesized using a structured narrative approach, with relevant SANRA quality-assessment domains considered during manuscript preparation and critical appraisal. Results: Piceatannol modulates multiple mechanisms implicated in obesity-associated metabolic dysfunction. In vitro studies demonstrate suppression of adipogenesis, attenuation of inflammatory and oxidative responses, and improvement in adipocyte metabolism and insulin signaling through pathways including AMPK, SIRT1, NF-κB, PI3K/Akt, MAPKs, and PPARγ. Selected animal studies have reported improvements in specific measures of weight gain, adiposity, hepatic lipid accumulation, glucose regulation, and inflammatory or oxidative markers; however, these findings vary across models and endpoints and have not been consistently replicated. A limited number of direct experimental comparisons have identified differences between piceatannol and resveratrol in selected biological endpoints. However, these findings are specific to the investigated models and experimental conditions and do not establish overall superiority in antioxidant, anti-inflammatory, or metabolic activity. No direct clinical comparisons are currently available to establish relative efficacy or safety. Preliminary randomized clinical studies using purified piceatannol have reported improvements in insulin resistance indices and blood pressure in selected populations, although findings remain inconsistent across

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metabolic outcomes. Studies involving piceatannol-rich passion fruit seed extracts have also reported beneficial effects on selected health-related outcomes; however, these effects cannot be attributed exclusively to piceatannol because of the presence of other bioactive constituents. Overall, human evidence remains limited by small sample sizes, heterogeneous study designs, and short intervention durations. Limited oral bioavailability and extensive phase II metabolism further constrain translation, while preliminary formulation studies suggest improvements in selected physicochemical or preclinical absorption parameters without establishing enhanced human systemic exposure, target-tissue delivery, or clinical efficacy. Conclusions: Piceatannol is a naturally occurring stilbene with experimentally observed biological activities relevant to several pathways implicated in obesity-associated metabolic dysfunction. Although cellular studies provide mechanistic and functional evidence, animal investigations remain relatively few and heterogeneous, with variable effects across metabolic outcomes. Preliminary human studies have reported changes in selected cardiometabolic and molecular biomarkers, but these findings do not establish clinically meaningful anti-obesity efficacy or superiority over resveratrol. Future research should prioritize standardized formulations, pharmacokinetic and dose–response characterization, independent preclinical replication, long-term safety evaluation, and adequately powered randomized controlled trials assessing clinically relevant metabolic outcomes.

Keywords: piceatannol; obesity; adipose tissue dysfunction; insulin resistance; metabolic inflammation; oxidative stress; resveratrol; polyphenols; adipogenesis; nutraceuticals

1. Introduction

Obesity has emerged as one of the most pressing global health challenges of the twenty-first century, affecting individuals across all age groups and representing a major contributor to chronic disease, disability, and premature mortality worldwide [1–5]. Beyond excessive body weight accumulation, obesity is now recognized as a complex systemic disorder characterized by adipose tissue dysfunction, chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, and impaired metabolic homeostasis. These interconnected abnormalities promote insulin resistance and contribute to the development of type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disease (CVD), and numerous other obesity-related complications [3,5]. Despite substantial advances in obesity management through lifestyle interventions, pharmacotherapy, and bariatric surgery, important therapeutic challenges remain, stimulating increasing interest in complementary nutritional strategies capable of simultaneously targeting multiple pathogenic mechanisms involved in metabolic dysfunction [6].

Among naturally occurring dietary bioactive compounds, polyphenols have attracted considerable attention because of their pleiotropic biological activities and their capacity to modulate multiple pathways implicated in metabolic health [7]. Within this diverse class, piceatannol (3,3′,4,5′-tetrahydroxystilbene), a naturally occurring stilbene structurally related to resveratrol, has emerged as an attractive candidate owing to its multifaceted biological actions affecting adipose tissue biology, inflammation, oxidative stress, mitochondrial function, and insulin sensitivity [8]. Moreover, the substantial body of experimental and clinical evidence generated since the comprehensive review by Kershaw et al. [8] has considerably expanded current understanding of the metabolic actions and translational potential of piceatannol, highlighting the need for an updated and integrated evaluation of the available literature. Accordingly, the present narrative review critically synthesizes current mechanistic, preclinical, clinical, and pharmacokinetic evidence regarding the role

of piceatannol in obesity and metabolic disease, identifies existing knowledge gaps, and discusses future perspectives for its clinical translation.

1.1. Obesity and Metabolic Dysfunction: A Growing Global Burden

Obesity is a major contributor to non-communicable disease worldwide. In 2022, approximately 2.5 billion adults were overweight, including more than 890 million living with obesity [9]. Its prevalence has increased markedly over recent decades, with projections indicating a continuing substantial global burden [1,9–11]. Beyond excess adiposity, obesity involves inflammatory, oxidative, and metabolic disturbances that increase the risk of insulin resistance, T2DM, MASLD, and CVD [1,3,12,13].

Lifestyle interventions remain central to obesity management, while incretin-based pharmacotherapies, including glucagon-like peptide-1 (GLP-1) receptor agonists and dual incretin receptor agonists, and bariatric surgery offer important benefits for appropriately selected patients [14–19]. Beyond their established effects on body weight and glycemic regulation, incretin-based therapies have demonstrated favorable effects on several components of obesity-associated metabolic dysfunction, including reductions in systemic inflammatory biomarkers, improvements in ectopic lipid accumulation, and modulation of adipose-tissue inflammatory responses. Therefore, their therapeutic benefits should not be interpreted as being restricted to appetite suppression or weight reduction. Nevertheless, important challenges remain regarding treatment costs and accessibility, gastrointestinal adverse effects, long-term treatment persistence and adherence, weight regain following discontinuation, and preservation of lean mass during substantial weight loss. These considerations, together with the multifactorial nature of obesity-associated metabolic dysfunction, provide a rationale for investigating additional nutritional and pharmacological approaches. However, such investigations should be considered complementary to, rather than replacements of, established evidence-based obesity treatments. Piceatannol is of interest because experimental studies suggest effects on adipocyte function, inflammatory signaling, and glucose–lipid metabolism; whether these effects provide clinically meaningful benefits, either independently or alongside established therapies, remains to be demonstrated.

1.2. Adipose Tissue Dysfunction as a Driver of Metabolic Disease

Adipose tissue is an endocrine and immunometabolic organ that contributes to systemic metabolic homeostasis through lipid storage, adipokine secretion, and interactions with immune and metabolic signaling pathways [20,21]. Under conditions of sustained nutrient excess, impaired adipose tissue expandability, adipocyte hypertrophy, inflammatory signaling, and metabolic stress may contribute to insulin resistance and obesity-associated complications [20–24]. Importantly, physiological adipogenesis may support metabolically appropriate lipid storage, whereas restricted adipocyte recruitment and excessive hypertrophy can favor ectopic lipid accumulation. Therefore, inhibition of adipogenesis should not automatically be interpreted as metabolically beneficial, since its consequences depend on adipose tissue depot, physiological context, and the balance between healthy adipocyte expansion and pathological hypertrophy [20–24]. The underlying pathophysiological mechanisms are examined in greater detail in Section 4.

Macrophage recruitment and altered secretion of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and adiponectin are associated with activation of nuclear factor kappa B (NF-κB), c-Jun N-terminal kinase (JNK), and related inflammatory pathways [20,22,23,25]. These processes identify biologically relevant endpoints for evaluating piceatannol, including adipogenesis, AMPK-associated metabolic regulation, inflammatory mediator production, oxidative stress, and insulin signaling. The compound-specific experimental evidence is examined in Section 5.

1.3. Natural Polyphenols and Stilbenes as Emerging Metabolic Modulators

Natural dietary polyphenols have attracted considerable attention as complementary nutritional strategies for the prevention and management of obesity and its associated metabolic disorders because of their potential to modulate multiple interconnected biological processes involved in energy homeostasis and metabolic regulation [26,27]. Widely distributed in fruits, vegetables, tea, coffee, cocoa, whole grains, nuts, and medicinal plants, polyphenols comprise several structurally diverse classes, including flavonoids, phenolic acids, lignans, and stilbenes [26,27]. Experimental and clinical evidence suggests that selected polyphenols may influence glucose and lipid metabolism, insulin sensitivity, mitochondrial function, oxidative balance, and inflammatory responses through coordinated regulation of metabolic signaling pathways [28,29].

Among the various classes of polyphenols, stilbenes have emerged as particularly attractive candidates because of their broad spectrum of biological activities. Resveratrol is the most extensively investigated stilbene and has demonstrated beneficial effects in numerous experimental models of obesity, T2DM, CVD, and age-related disorders [30,31]. However, its limited bioavailability and variable clinical efficacy have stimulated interest in structurally related stilbenes with potentially distinct pharmacological properties and biological activities [30,31]. Among these compounds, piceatannol has attracted increasing attention as a potential modulator of metabolic dysfunction, providing the rationale for a more focused examination of its biological properties and translational potential [32,33].

1.4. Piceatannol: A Promising Multifunctional Stilbene for Metabolic Health

Piceatannol has emerged as a promising naturally occurring stilbene owing to its potential to modulate several interconnected molecular pathways implicated in obesity-associated metabolic dysfunction [32,33]. Experimental investigations indicate that piceatannol may influence adipocyte differentiation, inflammatory signaling, oxidative stress, mitochondrial homeostasis, and insulin responsiveness through multiple regulatory mechanisms [34–36]. These pleiotropic biological activities provide a mechanistic basis for investigating piceatannol as a potential complementary nutritional strategy for obesity-related metabolic disorders, although their clinical relevance remains to be established.

Since the publication of the comprehensive review by Kershaw et al. [8], additional mechanistic investigations have expanded current understanding of the molecular targets and signaling pathways involved in the metabolic actions of piceatannol. In parallel, preclinical studies, pharmacokinetic investigations, formulation strategies aimed at improving bioavailability, and human clinical studies have provided further insights into its biological activity and translational potential [34–36]. Nevertheless, important uncertainties remain concerning its clinical efficacy, optimal dosing, long-term safety, systemic bioavailability, and the extent to which experimental findings can be translated into clinically meaningful outcomes. Consequently, an updated critical synthesis integrating mechanistic, preclinical, pharmacokinetic, and clinical evidence is warranted to clarify the current state of knowledge and identify priorities for future research.

1.5. Rationale and Objectives of the Review

1.5.1. Existing Knowledge Gaps

Despite the rapidly expanding body of research on piceatannol, several important knowledge gaps continue to limit its clinical translation for obesity and related metabolic disorders. Although numerous cellular and animal studies have demonstrated that piceatannol may modulate adipose tissue biology, metabolic inflammation, oxidative stress, mitochondrial homeostasis, lipid metabolism, and insulin signaling, these findings have largely been reported in isolation, with most investigations focusing on individual molecular path-

ways or specific biological processes rather than integrating their collective contribution to obesity-associated metabolic dysfunction.

Furthermore, although previous reviews have summarized the chemistry, pharmacology, biological activities, and therapeutic potential of piceatannol in diverse pathological conditions, none has comprehensively integrated the available mechanistic, preclinical, pharmacokinetic, and clinical evidence specifically within the context of adipose tissue dysfunction, metabolic inflammation, insulin resistance, and obesity-related metabolic disorders [8,34–36]. Consequently, the current understanding of the metabolic actions of piceatannol remains fragmented, limiting identification of the principal mechanisms through which it may improve metabolic health.

In addition, human evidence remains limited and heterogeneous. Existing clinical studies differ considerably in sample size, formulation, dosage, intervention duration, study population, and outcome measures, making direct comparisons difficult and preventing definitive conclusions regarding clinical efficacy. Important questions also remain concerning bioavailability, extensive phase II metabolism, tissue distribution, optimal dosing strategies, long-term safety, and the contribution of circulating metabolites to the biological effects observed in vivo. Collectively, these limitations highlight the need for an updated and critical synthesis of the available evidence while identifying priorities for future translational research.

1.5.2. Review Objectives and Translational Perspective

Obesity is a multifactorial disease driven by complex interactions among adipose tissue dysfunction, chronic inflammation, oxidative stress, mitochondrial dysfunction, dysregulated lipid metabolism, and insulin resistance. Consequently, effective preventive and therapeutic strategies increasingly require modulation of multiple interconnected pathogenic pathways rather than a single molecular target.

Accumulating evidence suggests that piceatannol may exert pleiotropic biological effects through coordinated regulation of adipogenesis, lipid metabolism, inflammatory responses, mitochondrial function, oxidative balance, glucose homeostasis, and insulin signaling. These diverse actions could support its potential as a complementary nutritional strategy for obesity-associated metabolic disorders. However, the available evidence has not previously been critically synthesized within a unified framework integrating mechanistic insights from cellular studies with findings from animal models, human clinical investigations, pharmacokinetic studies, formulation strategies, and translational considerations.

Therefore, the present narrative review provides a comprehensive and critical evaluation of the current evidence regarding the potential role of piceatannol in obesity and metabolic disease. Specifically, this review aims to: (i) summarize the chemistry, dietary sources, bioavailability, metabolism, and pharmacokinetic properties of piceatannol; (ii) critically evaluate the molecular mechanisms through which piceatannol could modulate adipose tissue dysfunction, metabolic inflammation, and insulin resistance; (iii) synthesize evidence from in vitro studies, experimental animal models, and human clinical trials; (iv) discuss current translational challenges, including strategies to improve bioavailability and clinical applicability; and (v) identify key knowledge gaps and future research priorities necessary to determine whether piceatannol warrants further investigation as a potential intervention for obesity-associated metabolic dysfunction.

2. Literature Review Approach and Evidence Synthesis

2.1. Literature Search Strategy

A structured literature search was conducted to identify relevant evidence across the principal research domains addressed in this narrative review. The search strategy

was designed to capture mechanistic, translational, and clinical evidence concerning the biological activities of piceatannol, with particular emphasis on adipose tissue biology, insulin resistance, lipid metabolism, oxidative stress, and inflammatory signaling pathways. The literature search was designed to ensure broad coverage of the available evidence relevant to the objectives of this narrative review rather than exhaustive identification of all potentially eligible publications, as would be expected in a systematic review.

2.1.1. Databases Searched

Relevant literature was retrieved from four major electronic databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, and Google Scholar. These databases were selected because they provide extensive coverage of biomedical, nutritional, pharmacological, and life sciences research. To maximize the comprehensiveness of the search, additional studies were identified through manual examination of the reference lists of relevant articles and reviews.

2.1.2. Search Period

The literature search included publications available from database inception through 31 August 2026. No restrictions regarding publication year were imposed in order to capture both foundational and contemporary studies addressing the biological and therapeutic effects of piceatannol.

2.1.3. Search Terms

Search strategies were developed using combinations of free-text keywords and, where applicable, database-specific controlled vocabulary. The primary search term was "piceatannol," which was combined with terms related to obesity, metabolic dysfunction, and associated molecular mechanisms. Representative keywords included "obesity," "adipogenesis," "adipose tissue," "inflammation," "insulin resistance," "metabolic syndrome," "type 2 diabetes," "AMPK," and "oxidative stress." To improve coverage of hepatic manifestations of metabolic dysfunction, relevant terminology also included "metabolic dysfunction-associated steatotic liver disease" (MASLD), "non-alcoholic fatty liver disease" (NAFLD), "steatotic liver disease," "fatty liver," and "hepatic steatosis," where applicable to the searches performed. Additional combinations included "piceatannol AND metabolic health," "piceatannol AND adipocyte differentiation," and "piceatannol AND chronic inflammation." For PubMed/MEDLINE, free-text terms were distinguished from any Medical Subject Headings (MeSH) actually employed, with the corresponding field tags specified in the complete search strategy. Search syntax was adapted to the indexing requirements and functionalities of each database.

2.2. Eligibility Criteria

Eligible studies were selected according to predefined inclusion and exclusion criteria established before the screening process. The objective was to identify studies that directly examined the effects of piceatannol on metabolic regulation, obesity-related outcomes, inflammatory pathways, oxidative stress, or associated molecular mechanisms.

2.2.1. Inclusion Criteria

Studies were considered eligible if they were original research articles published in peer-reviewed journals and investigated piceatannol as a primary compound of interest. Included studies comprised in vitro experiments exploring cellular and molecular mechanisms, animal studies evaluating physiological and metabolic outcomes, and human clinical investigations examining the effects of piceatannol on metabolic, inflammatory, cardiovas-

cular, or endocrine parameters. Mechanistic studies focusing on signaling pathways, gene expression, protein regulation, or cellular responses associated with metabolic health were also included. Only articles published in the English language were considered eligible for inclusion.

For the purposes of evidence evaluation, studies investigating purified or isolated piceatannol were distinguished from those evaluating piceatannol-rich botanical extracts or other multicomponent plant-derived preparations. Studies involving botanical preparations were considered relevant when piceatannol was identified as a principal constituent or a major focus of the investigation and the reported outcomes were pertinent to the objectives of this review. However, findings obtained with such preparations were not considered equivalent to compound-specific evidence, because additional phytochemicals and matrix constituents may independently or collectively contribute to the observed biological effects.

2.2.2. Exclusion Criteria

Publications were excluded if they were not written in English or did not contain original experimental data. Conference abstracts, editorials, commentaries, letters to the editor, and opinion articles were excluded due to their limited methodological information and lack of primary findings. Narrative reviews, systematic reviews, and meta-analyses were not included in the evidence synthesis, although they were consulted for background information and identification of additional references. Studies primarily focused on outcomes unrelated to obesity, metabolic dysfunction, inflammation, oxidative stress, or insulin resistance were also excluded. Furthermore, studies in which piceatannol was not evaluated as a principal intervention or exposure were not considered relevant for inclusion.

2.3. Study Selection and Data Extraction

2.3.1. Screening Process

The study selection process consisted of a sequential evaluation of titles, abstracts, and full-text articles. Initially, all records retrieved from the electronic databases were screened for relevance based on their titles and abstracts. Publications that were clearly unrelated to piceatannol or metabolic health were excluded during this stage. Full-text articles were subsequently assessed for eligibility according to the predefined inclusion and exclusion criteria. Additional records identified through manual screening of reference lists were subjected to the same evaluation process before inclusion in the review.

2.3.2. Data Extraction Approach

Relevant study characteristics and findings were extracted using a standardized approach from the studies selected for inclusion in the narrative synthesis. Information collected included study design, experimental model, population or cell type investigated, sample size, intervention characteristics, dosage and duration of piceatannol exposure, and primary outcomes assessed. Particular attention was given to data relating to adipogenesis, adipose tissue function, inflammation, oxidative stress, glucose metabolism, insulin sensitivity, lipid homeostasis, body weight regulation, and associated molecular signaling pathways. Information regarding mechanisms involving 5′-adenosine monophosphate-activated protein kinase (AMPK), NF-κB, peroxisome proliferator-activated receptors (PPARs), mitogen-activated protein kinases (MAPKs), and other relevant metabolic regulators was extracted whenever available.

To strengthen pharmacological interpretation, particular attention was also given to the nature of the investigated preparation, distinguishing purified piceatannol from piceatannol-rich botanical extracts. Where reported, information concerning compound purity, botanical source, extraction or formulation characteristics, piceatannol content,

accompanying phytochemical constituents, and administered dose was considered. For botanical preparations, the total extract dose was distinguished from the corresponding piceatannol dose whenever sufficient compositional information was available. These characteristics were considered when comparing experimental findings and evaluating the extent to which reported biological effects could be attributed specifically to piceatannol.

2.3.3. Evidence Synthesis Strategy

Given the substantial heterogeneity among available studies in terms of experimental models, intervention protocols, outcome measures, and methodological approaches, a quantitative meta-analysis was not considered appropriate. Instead, findings were synthesized narratively and organized according to major thematic areas. The evidence was grouped into sections addressing the chemistry and biological characteristics of piceatannol, its effects on adipocyte biology and adipogenesis, its role in regulating inflammation and oxidative stress, its influence on glucose metabolism and insulin sensitivity, and its potential applications in obesity-related metabolic disorders. Clinical evidence, pharmacokinetic considerations, safety data, and future translational perspectives were also integrated into the overall synthesis to provide a comprehensive overview of the field.

Although relevant review articles were consulted to provide background information, contextualize the current state of knowledge, and identify additional primary studies, the evidence synthesis presented in this review was based primarily on original in vitro, animal, and human investigations.

An additional consideration during evidence synthesis was the distinction between compound-specific and botanical matrix-associated effects. Findings obtained with purified piceatannol were interpreted as evidence concerning the biological activity of the compound investigated, whereas findings from piceatannol-rich extracts were evaluated as preparation-specific evidence. In the latter case, potential contributions from other phytochemicals, differences in matrix composition, and possible interactions among constituents were considered when interpreting the reported outcomes. Consequently, beneficial effects observed following administration of botanical extracts were not attributed exclusively to piceatannol unless supported by appropriate compound-specific experimental comparisons.

To avoid conflating different levels of evidence, the findings were interpreted according to their experimental context and degree of causal and clinical support. Mechanistic plausibility was distinguished from experimental associations between piceatannol exposure and changes in molecular signaling pathways. Functional cellular evidence was considered separately from physiological or metabolic outcomes demonstrated in animal models. Animal findings were further evaluated according to the extent of independent replication, consistency across experimental models, and relevance of the administered doses and exposure conditions. Human findings were distinguished according to whether they involved pharmacokinetic measurements, molecular or cardiometabolic biomarkers, or clinically meaningful health outcomes. Importantly, changes in surrogate biomarkers were not regarded as evidence of established clinical efficacy, and short-term tolerability was not considered sufficient to establish long-term safety. Accordingly, conclusions were formulated in relation to the specific level of evidence available, with particular caution when extrapolating cellular or animal findings to human obesity and related metabolic disorders.

For the interpretation of animal studies, particular attention was given to distinguishing physiological efficacy from mechanistic validation. Changes in body weight, adiposity, fasting glycemia, glucose tolerance, circulating lipids, hepatic triglyceride accumulation, or gene and protein expression were considered evidence of the specific outcomes measured rather than proof that molecular pathways identified in cultured cells mediated the observed responses in vivo. Mechanistic validation was considered to require more

direct evidence, including characterization of target-tissue exposure to piceatannol and its metabolites, demonstration of molecular target engagement, appropriate pathway-specific pharmacological or genetic interventions, tissue-specific metabolic flux measurements, or experimental mediation analyses. In the absence of such evidence, similarities between cellular and animal findings were interpreted as mechanistic compatibility or biological plausibility rather than confirmation of a shared causal mechanism.

For glucose-related outcomes, particular attention was given to distinguishing fasting glycemia, glucose tolerance, insulin secretion, surrogate indices of insulin resistance, and directly measured insulin sensitivity. Fasting glucose was interpreted as an indicator of glycemic status rather than a direct measure of insulin responsiveness. Glucose-tolerance tests were considered integrated assessments of glucose handling that may reflect differences in glucose absorption, insulin secretion, hepatic glucose production, and peripheral glucose disposal. Homeostatic model assessment of insulin resistance (HOMA-IR) was interpreted as a fasting-state surrogate index rather than a direct measurement of insulin sensitivity, whereas insulin-tolerance tests were considered dynamic but indirect assessments influenced by counterregulatory responses. Hyperinsulinemic–euglycemic clamp measurements, where available, were distinguished as more direct assessments of insulin-mediated glucose disposal and suppression of endogenous glucose production, depending on the protocol employed. Consequently, conclusions regarding improved insulin sensitivity were restricted to the specific measurements performed and were not inferred solely from reductions in fasting glucose or improvements in glucose tolerance.

2.4. Review Methodology and Limitations

2.4.1. Narrative Review Framework

The present study was designed as a structured narrative review aimed at providing a critical and integrated synthesis of mechanistic, preclinical, pharmacokinetic, and clinical evidence concerning piceatannol and its potential role in obesity-associated metabolic dysfunction. Although structured database searches, predefined eligibility criteria, sequential relevance assessment, and standardized data extraction procedures were employed to enhance methodological transparency and consistency, the literature search was intended to provide broad coverage of evidence relevant to the objectives of the review rather than exhaustive identification of all potentially eligible publications, as would be expected in a systematic review. Study selection was guided by predefined topical relevance and the contribution of individual investigations to the principal mechanistic, metabolic, and translational questions addressed. Accordingly, the present work should not be interpreted as a systematic review, and no claim of exhaustive evidence identification or formal systematic risk-of-bias assessment is made. This structured narrative approach was considered appropriate because the available literature encompasses heterogeneous experimental designs, including cellular studies, animal investigations, pharmacokinetic assessments, and a limited number of human clinical trials, making an integrated qualitative synthesis more suitable for the objectives of the present review.

2.4.2. Consideration of SANRA Quality-Assessment Domains

To support the clarity, scientific quality, and transparency of the present structured narrative review, relevant domains of the Scale for the Assessment of Narrative Review Articles (SANRA) were considered during manuscript preparation and critical appraisal [37–39]. Particular attention was given to the justification of the review's importance, explicit formulation of its objectives, description of the literature search, appropriate referencing, scientific reasoning, and presentation of relevant evidence. SANRA is a quality-assessment instrument developed for evaluating narrative review articles and does not constitute a formal

reporting guideline or a methodological framework for conducting literature searches, study selection, or evidence synthesis. Accordingly, the structured literature search, relevance-based study selection, and narrative integration of findings described in Sections 2.1–2.3 were undertaken as components of the review's methodological approach independently of SANRA. Consideration of SANRA domains was intended to support the overall quality and transparency of the manuscript rather than to imply adherence to a prescribed review methodology or formal systematic-review reporting standards.

Unlike systematic reviews, the objective of the present review was not to identify every potentially eligible publication or to perform a formal quantitative synthesis of the evidence, but rather to critically integrate and interpret the available mechanistic, preclinical, and the clinical literature relevant to the role of piceatannol in obesity prevention and management [37–39].

2.4.3. Limitations of Narrative Evidence Synthesis

Several limitations inherent to narrative reviews should be acknowledged. Unlike systematic reviews and meta-analyses, narrative reviews are more susceptible to selection bias and subjective interpretation of findings. Although a structured literature search strategy and predefined eligibility criteria were employed, the present review adopted a relevance-based approach to study selection, prioritizing investigations that directly addressed its principal mechanistic, preclinical, pharmacokinetic, and clinical objectives rather than attempting exhaustive identification of all potentially eligible publications. Consequently, potentially relevant studies may have been overlooked, and the selection process may have introduced selection bias. Furthermore, no formal systematic risk-of-bias assessment using standardized study-design-specific instruments was performed. Therefore, the methodological quality and certainty of the available evidence were evaluated narratively, considering study design, experimental limitations, consistency of findings, and translational relevance, rather than through a formal systematic evidence-grading framework. In addition, substantial heterogeneity exists among the available studies regarding experimental models, dosages, intervention durations, analytical methods, and outcome measurements, limiting direct comparisons across investigations. Another important limitation is that much of the current evidence concerning piceatannol originates from in vitro and animal studies, whereas human clinical evidence remains relatively limited. Consequently, caution is warranted when extrapolating mechanistic findings from experimental models to clinical practice. Furthermore, differences in bioavailability, metabolism, formulation characteristics, and study populations may contribute to inconsistencies among findings and complicate translation to real-world applications. Despite these limitations, the present structured narrative review provides an integrated and critical synthesis of evidence selected for its relevance to the review objectives, offering a perspective on the potential role of piceatannol as a multifunctional modulator of obesity-associated metabolic dysfunction and chronic inflammation.

Finally, as with any narrative review, the potential influence of publication bias should be acknowledged. Studies demonstrating positive or statistically significant outcomes are more likely to be published than investigations reporting null or negative findings, potentially resulting in an overrepresentation of favorable evidence and an inflated perception of therapeutic efficacy [39–42]. In addition, selective outcome reporting and dissemination bias may further compromise the completeness, transparency, and overall balance of the available literature [39–42]. These inherent limitations underscore the need for greater methodological rigor in future research, including standardized experimental protocols, optimization of piceatannol formulations to improve bioavailability and stability, adequately

powered randomized controlled trials, and well-designed translational studies to more definitively establish the clinical efficacy, safety, and therapeutic potential of piceatannol.

3. Chemistry, Dietary Sources, Bioavailability, and Metabolism of Piceatannol

3.1. Chemical Structure and Physicochemical Properties

Piceatannol (3,3′,4,5′-trans-tetrahydroxystilbene) is a naturally occurring polyphenolic compound belonging to the stilbene family. Structurally, it consists of two aromatic rings connected through a trans-ethylene bridge and possesses four hydroxyl groups distributed across its phenolic rings [43–45]. The molecular formula of piceatannol is $C_{14}H_{12}O_4$, corresponding to a molecular weight of 244.24 g/mol. The additional hydroxyl group relative to resveratrol distinguishes piceatannol structurally and contributes to differences in its physicochemical properties and biological activity [43–45]. The compound exists predominantly in the biologically active trans-isomeric form, although cis-isomers may be generated under conditions of prolonged light exposure or chemical instability [46]. In Figure 1, the chemical structure, dietary sources, and absorption, distribution, metabolism, and excretion (ADME) of piceatannol are illustrated.

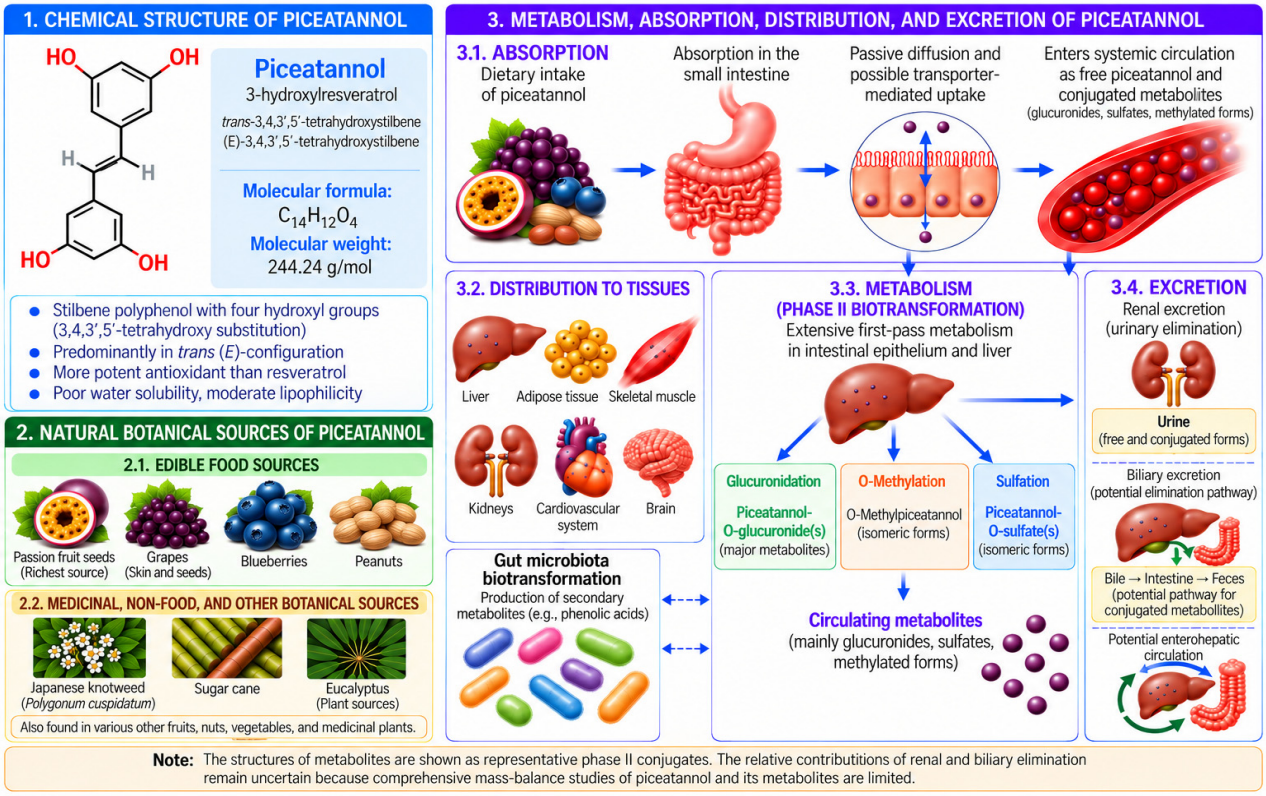


Figure 1. Chemical structure, dietary sources, and absorption, distribution, metabolism, and excretion (ADME) of piceatannol.

Piceatannol is structurally similar to resveratrol (3,5,4′-trihydroxystilbene), differing only by the presence of an additional hydroxyl group at the 3′ position. This seemingly minor structural modification substantially influences its physicochemical and biological properties [47–49]. Experimental and computational structure–activity investigations suggest that the additional hydroxyl group may influence hydrogen-atom donation, electron-transfer reactions, and phenoxyl radical stabilization [47–49]. Although greater radical-scavenging activity has been reported for piceatannol in selected direct comparative chemical

assays, these findings are assay-dependent and do not establish superior antioxidant activity across biological systems or in vivo.

Piceatannol exhibits moderate lipophilicity (calculated logP ≈ 2.64), enabling its partitioning into phospholipid membranes, while maintaining sufficient hydrophilicity through its four hydroxyl groups [50,51]. This amphipathic nature allows piceatannol to interact preferentially with the polar headgroup region of lipid bilayers via hydrogen-bonding interactions, while still penetrating the membrane interface [50,51].

Similarly to many dietary polyphenols, piceatannol exhibits relatively poor aqueous solubility, which limits its dissolution in gastrointestinal fluids and may reduce oral absorption [52]. In addition, the catechol-containing structure of piceatannol renders it susceptible to oxidative degradation, particularly under conditions that promote oxidation, leading to the formation of oxidation products and oligomeric derivatives [53]. Consequently, these physicochemical characteristics, together with extensive phase II metabolism, contribute to variable systemic exposure following oral administration and have stimulated investigations of formulation strategies, including cyclodextrin inclusion complexes to address solubility limitations and evaluate potential improvements in oral absorption. Although enhanced absorption has been reported for a piceatannol–cyclodextrin complex in rats, corresponding improvements in human systemic exposure, target-tissue delivery, or clinical efficacy have not been established [52,54].

It is important to distinguish the different stability and pharmacokinetic properties relevant to piceatannol. Chemical stability refers to the resistance of the parent compound to chemical degradation or structural transformation under defined conditions, including variations in pH, temperature, light exposure, and storage. Oxidative stability represents a more specific aspect of chemical stability and describes resistance to oxidation, which may be particularly relevant to the catechol-containing structure of piceatannol. In contrast, metabolic stability refers to the susceptibility of piceatannol to enzyme-mediated biotransformation, particularly intestinal and hepatic conjugation reactions, and should not be inferred from chemical or oxidative stability measurements. Oral bioavailability is a distinct pharmacokinetic parameter describing the fraction of an orally administered dose that reaches systemic circulation as unchanged parent compound. Consequently, improvements in chemical stability, oxidative protection, aqueous solubility, or formulation dissolution do not necessarily indicate enhanced metabolic stability or oral bioavailability. These properties require different experimental approaches and should be evaluated independently.

3.2. Dietary and Non-Dietary Botanical Sources of Piceatannol

Piceatannol occurs naturally in various botanical materials, including edible foods, agricultural by-products, medicinal plants, and other non-food plant species. For clarity, these sources should be distinguished according to their principal dietary or non-dietary relevance. Edible sources include grapes, blueberries, peanuts, and passion fruit-derived materials, whereas other plants, such as Japanese knotweed (*Reynoutria japonica*; syn. *Polygonum cuspidatum*) and certain *Eucalyptus* species, are primarily relevant as medicinal, phytochemical, or non-food botanical sources. Piceatannol concentrations vary considerably according to plant species, cultivar, geographic origin, environmental conditions, maturation stage, and processing methods. Importantly, the identification of piceatannol in a botanical material does not necessarily indicate substantial dietary exposure, and the presence of this compound in medicinal or non-food plants should not be interpreted as evidence of their suitability for routine dietary consumption.

3.2.1. Passion Fruit Seeds

Passion fruit (*Passiflora edulis*) seeds represent one of the richest known dietary sources of piceatannol. Interest in passion fruit seeds has increased substantially following the discovery that they contain exceptionally high concentrations of this stilbene compared with most other edible plant materials [33,55–57]. Traditionally regarded as a by-product of juice production, passion fruit seeds are now recognized as a valuable source of bioactive compounds with potential nutraceutical, and pharmaceutical applications. Their abundance, sustainability, and rich phytochemical profile have promoted their valorization as a source of bioactive compounds for functional foods, nutraceuticals, cosmetics, and pharmaceuticals applications [33,55–57].

Studies investigating piceatannol-rich extracts derived from *Passiflora edulis* seeds have reported antioxidant, anti-inflammatory, and metabolic effects in selected experimental models [8,33,58]. However, these extracts are chemically complex preparations containing piceatannol alongside other phenolic constituents, including scirpusin B, a stilbene dimer, and additional polyphenolic compounds. Their composition and relative constituent concentrations may vary depending on the botanical material and extraction procedures. Consequently, biological effects observed following administration of passion fruit seed extracts should be interpreted as preparation-specific findings rather than direct evidence of the pharmacological activity of purified piceatannol. These preparations remain of interest for the development of functional foods and nutraceuticals, although their potential metabolic benefits require further investigation using chemically characterized extracts and appropriate compound-specific comparisons.

3.2.2. Grapes

Grapes (*Vitis vinifera*) represent another important natural source of piceatannol, although concentrations are generally lower than those found in passion fruit seeds [59,60]. Similarly to resveratrol, piceatannol is predominantly localized in grape skins and seeds, where it functions as a stilbene phytoalexin involved in the plant's defense against biotic and abiotic stress [59,60]. Its accumulation varies considerably among grape cultivars and is influenced by environmental conditions, with fungal infection and ultraviolet irradiation acting as potent elicitors of stilbene biosynthesis, leading to increased piceatannol production [59,60].

Wine and grape-derived products have attracted considerable scientific attention owing to their diverse polyphenolic composition, including the presence of stilbenes [35,61,62]. Although resveratrol is generally the predominant stilbene in grapes and red wine, piceatannol has also been identified as a constituent of their phytochemical profile. However, its occurrence in these products should not be interpreted as evidence that conventional dietary consumption provides sufficient piceatannol exposure to exert clinically meaningful biological effects. Quantitative concentrations may vary substantially according to grape cultivar, environmental conditions, processing, and product characteristics, while reliable estimates of habitual intake and systemic exposure remain insufficient. Furthermore, although grape-derived products have been investigated for their potential cardiometabolic effects, these outcomes cannot be attributed specifically to piceatannol without direct compound-specific evidence [35,61,62].

3.2.3. Blueberries

Blueberries (*Vaccinium* spp.) and several other berry fruits have been reported to contain piceatannol, generally at lower concentrations than those identified in piceatannol-rich passion fruit seeds and selected grape-derived materials [63,64]. These fruits also contain numerous other phenolic constituents, particularly anthocyanins, which contribute

to their complex phytochemical composition. Although berry consumption has been investigated in relation to cardiometabolic health, oxidative stress, and glucose regulation, the potential contribution of piceatannol to these outcomes remains uncertain. In particular, the detection of piceatannol in blueberries does not establish that habitual consumption produces biologically relevant systemic concentrations or that observed health effects can be attributed to this individual compound. Such conclusions would require quantitative food-composition data, dietary exposure estimates, and direct human pharmacokinetic or intervention evidence [63,64].

Although blueberries may contribute to dietary intake of various polyphenolic compounds, the quantitative contribution of their piceatannol content to habitual dietary exposure remains insufficiently characterized. Consequently, no conclusions can currently be drawn regarding the extent to which conventional blueberry consumption influences systemic piceatannol exposure or produces piceatannol-specific metabolic effects [63,65]. Accordingly, the cardiometabolic effects reported for whole berries, grapes, wine, or their polyphenol-rich preparations should not be extrapolated to piceatannol as an individual bioactive compound unless supported by direct compound-specific experimental or clinical evidence.

3.2.4. Peanuts

Peanuts (*Arachis hypogaea*) constitute another dietary source of piceatannol and related stilbenes [66,67]. Piceatannol has been identified in peanut kernels, skins, sprouts, and several peanut-derived products, with peanut skins generally exhibiting higher concentrations of phenolic compounds than kernels. Similarly to grapes, piceatannol and other stilbenes function as phytoalexins, and their biosynthesis can be markedly induced by biotic stress, particularly fungal infection, contributing to the plant's defense response [66,67].

Although peanuts are widely consumed, the quantitative contribution of conventional peanut intake to habitual dietary exposure to piceatannol remains uncertain because of limited food-composition and intake data [66,67]. Piceatannol concentrations may vary considerably among peanut tissues and products, particularly between kernels, skins, and sprouts. Moreover, the presence of piceatannol in peanut-derived materials does not establish that customary consumption produces systemic exposures comparable to those investigated using purified piceatannol or standardized piceatannol-rich preparations. Accordingly, clinically meaningful metabolic effects cannot be inferred from the occurrence of piceatannol in peanuts alone [66,67].

3.2.5. Medicinal, Non-Food, and Other Botanical Sources

In addition to edible food sources, piceatannol has been identified in several medicinal, non-food, and other botanical materials, including Japanese knotweed (*Reynoutria japonica* Houtt.; syn. *Polygonum cuspidatum*), *Eucalyptus* species, and various plants used in traditional medicinal systems [30,68]. These botanical materials should be distinguished from conventional dietary sources because their identification as reservoirs of piceatannol does not imply that they are routinely consumed as foods or that their consumption is appropriate or safe. Other reported plant sources include rhubarb (*Rheum* spp.) and sugar cane (*Saccharum officinarum*), whose dietary relevance depends on the specific plant part, preparation, and intended use [30,68]. Several of these species also contain resveratrol, pterostilbene, and other stilbene derivatives, reflecting related biosynthetic pathways. Their relevance to piceatannol research therefore lies primarily in botanical occurrence, phytochemical characterization, and potential compound isolation rather than demonstrated dietary exposure or clinical efficacy.

The growing interest in sustainable sources of bioactive compounds has stimulated efforts to valorize agricultural and food-processing by-products as alternative sources of piceatannol and other health-promoting phytochemicals [33,58]. In particular, piceatannol-rich residues such as passion fruit seeds have emerged as promising raw materials for the sustainable recovery of high-value stilbenes [33,58]. Advances in extraction and purification technologies, together with circular bioeconomy approaches, may facilitate the large-scale production of piceatannol for incorporation into functional foods, nutraceuticals, cosmetic formulations, and pharmaceutical products [69,70].

3.3. Absorption, Distribution, Metabolism, and Excretion

The biological effects of piceatannol depend not only on its intrinsic activity but also on its ADME characteristics [32,71–74]. Following oral administration, piceatannol appears to be absorbed predominantly in the small intestine. Although direct mechanistic studies are limited, its absorption is thought to occur mainly through passive transcellular diffusion, similar to other low-molecular-weight dietary stilbenes, while the contribution of transporter-mediated uptake remains to be established [32,71–74]. As with many plant-derived polyphenols, its oral bioavailability is influenced by multiple factors, including the food matrix, gastrointestinal environment, enzymatic metabolism, and interactions with the intestinal microbiota, all of which contribute to substantial inter-individual variability in systemic exposure [32,71–74].

Once absorbed, piceatannol enters the systemic circulation and undergoes rapid distribution to peripheral tissues, accompanied by extensive hepatic metabolism. Pharmacokinetic studies in rodents indicate a relatively large volume of distribution, suggesting broad tissue penetration, while experimental studies have demonstrated biological activity in metabolically important organs, including the liver, adipose tissue, skeletal muscle, kidneys, and the cardiovascular system [54,70,75]. However, direct quantitative data on tissue concentrations and long-term accumulation remain limited, highlighting the need for further biodistribution studies to better define the tissue-specific pharmacokinetics of piceatannol, and its potential role in modulating obesity-related pathways.

A substantial proportion of absorbed piceatannol undergoes extensive phase II metabolism in the intestinal epithelium and liver [71,72,75,76]. The principal biotransformation pathways include glucuronidation, sulfation, and catechol-O-methyltransferase (COMT)-mediated O-methylation, resulting in the formation of glucuronide, sulfate, and methylated metabolites that contribute to systemic exposure [71,72,75,76]. These conjugation reactions generally increase aqueous solubility and may facilitate elimination through renal and hepatobiliary pathways, although their relative quantitative contributions remain insufficiently characterized [71,72,75,76]. Although phase II metabolism has traditionally been regarded as a detoxification process, the possibility that certain piceatannol metabolites retain biological activity or exhibit pharmacokinetic properties distinct from those of the parent compound warrants further investigation [71,72,75,76].

An important unresolved question concerns the potential biological activity of circulating phase II metabolites and their contribution to the metabolic effects attributed to piceatannol. Following intestinal and hepatic biotransformation, piceatannol glucuronides and sulfates may represent important components of systemic exposure, while O-methylated derivatives contribute to its broader metabolic profile [71,72,75,76]. Although conjugation modifies the physicochemical properties and potentially the biological activity of the parent compound, these metabolites should not necessarily be regarded as pharmacologically inactive. Their possible effects on adipocyte function, inflammatory signaling, oxidative stress, and insulin sensitivity remain insufficiently characterized. A further mechanistic possibility involves localized enzymatic deconjugation of glucuronide and sulfate metabo-

lites through β-glucuronidase and sulfatase activities, respectively, potentially regenerating unconjugated piceatannol within specific tissue microenvironments. Such a process could theoretically influence local exposure to the parent compound, particularly in metabolically dysfunctional or inflamed tissues. However, direct experimental evidence demonstrating tissue-specific deconjugation of piceatannol metabolites, the concentrations of regenerated piceatannol, or their contribution to metabolic outcomes remains limited. Consequently, the intrinsic bioactivity of individual metabolites and their potential role as reservoirs for localized regeneration of the parent compound should be regarded as hypotheses requiring further experimental validation.

Following systemic distribution and metabolic transformation, piceatannol and its phase II metabolites may undergo elimination through renal and hepatobiliary pathways. Although urinary excretion of conjugated metabolites has been documented, comprehensive mass-balance studies quantifying the relative contributions of renal, biliary, and fecal elimination remain limited. Consequently, the predominant elimination route of piceatannol and its metabolites has not been conclusively established [71,72,75,76]. Animal studies also indicate a bidirectional interaction between piceatannol and the intestinal microbiota, as piceatannol supplementation can alter microbial community composition [77–79]. Although gut microorganisms are known to convert many dietary polyphenols and structurally related stilbenes into secondary metabolites with distinct pharmacokinetic and biological properties, direct characterization of microbiota-derived piceatannol metabolites remains scarce [80]. Accordingly, interindividual differences in gut-microbial composition may contribute to variability in piceatannol metabolism and physiological responsiveness, but this possibility requires confirmation in dedicated microbial-metabolism and human pharmacokinetic studies.

3.4. Pharmacokinetics in Experimental Models and Humans

Pharmacokinetic investigations have demonstrated that piceatannol is rapidly absorbed and extensively metabolized following oral administration. In rodent studies, peak plasma concentrations are typically reached within the first few hours after dosing, followed by a progressive decline as the compound undergoes phase II metabolism and subsequent elimination [54,71,72,75,81]. Representative quantitative findings further illustrate the available preclinical pharmacokinetic evidence. Following oral administration of piceatannol at 360 μmol/kg in rats, a maximum plasma concentration (C_{max}) of approximately 8.1 μM has been reported [8,72]. In a separate rat investigation employing intravenous administration at 10 mg/kg, the plasma elimination half-life was approximately 4.23 h, whereas the urinary elimination half-life was substantially longer (19.88 ± 5.66 h) [75]. These values were obtained under different experimental conditions and should not be combined into a single pharmacokinetic profile or extrapolated directly to human oral exposure. Furthermore, plasma concentrations of unconjugated piceatannol should be distinguished from concentrations of its glucuronidated, sulfated, and O-methylated metabolites, because these chemical species may differ in systemic exposure, tissue distribution, and biological activity [71,72,75,81]. Moreover, although experimental studies have demonstrated biological activity of piceatannol in metabolically relevant organs, including the liver, adipose tissue, skeletal muscle, and kidneys, comprehensive quantitative tissue biodistribution studies remain limited.

The pharmacokinetic profiles of piceatannol and resveratrol have been investigated in experimental studies, but the available evidence does not establish a consistent pharmacokinetic advantage for either compound across comparable administration conditions [54,71,72,75,81]. Both stilbenes undergo extensive intestinal and hepatic metabolism, including glucuronidation and sulfation, while piceatannol additionally un-

dergoes COMT-mediated O-methylation. Differences in systemic exposure reported across individual investigations should be interpreted in relation to species, dose, administration route, formulation, sampling schedule, and the distinction between unconjugated parent compounds and circulating metabolites. Consequently, higher exposure or greater metabolic stability observed under particular experimental conditions cannot be generalized to superior oral bioavailability or pharmacokinetic performance in humans. Comprehensive head-to-head pharmacokinetic investigations using standardized protocols are required to establish whether clinically relevant differences exist between the two compounds. Importantly, metabolic stability, systemic exposure, and oral bioavailability represent distinct pharmacokinetic concepts: reduced enzymatic biotransformation does not necessarily establish greater oral bioavailability, and differences in plasma exposure alone cannot distinguish changes in absorption from changes in presystemic metabolism or systemic clearance.

Human pharmacokinetic characterization of piceatannol remains insufficient. Although clinical intervention studies have administered purified piceatannol or piceatannol-containing preparations [82–84], these investigations do not provide adequately characterized plasma concentration–time profiles from which reliable human peak plasma concentrations (C_{max}), elimination half-lives ($t_{½}$), or separate exposure estimates for unconjugated piceatannol and its individual conjugated metabolites can be established. Consequently, quantitative human pharmacokinetic parameters should not be inferred from these studies. In contrast, experimental animal investigations have demonstrated systemic exposure to unconjugated piceatannol and extensive formation of glucuronidated, sulfated, and O-methylated metabolites following administration [54,71,72,75,81]. However, these findings are dependent on species, administered dose, route, formulation, and analytical methodology and cannot be directly extrapolated to humans. In particular, the detection of circulating metabolites or their urinary excretion does not independently establish their pharmacological activity, tissue availability, or relative contribution to systemic elimination. Dedicated human pharmacokinetic studies employing validated metabolite-specific analytical methods are therefore required to quantify parent-compound and metabolite exposure, determine elimination kinetics, and clarify the relationship between circulating concentrations and potential biological effects.

Factors such as age, sex, metabolic status, genetic polymorphisms affecting conjugation enzymes, dietary habits, and gut microbiota composition may all contribute to differences in piceatannol bioavailability and pharmacokinetics among individuals. In view of the above considerations, additional well-controlled human studies are needed to establish optimal dosing regimens and characterize long-term exposure patterns. Future pharmacokinetic investigations should also incorporate comprehensive mass-balance assessments to quantify urinary and fecal recovery of piceatannol and its metabolites, clarify the contribution of biliary elimination, and determine whether enterohepatic recirculation occurs to a clinically relevant extent. Furthermore, future studies should characterize the systemic exposure and tissue distribution of individual glucuronide, sulfate, and O-methylated metabolites alongside unconjugated piceatannol. Particular attention should be given to determining whether these metabolites exhibit intrinsic biological activity or undergo localized enzymatic deconjugation, potentially regenerating the parent compound within metabolically relevant tissues. Such investigations could help clarify the relationship between circulating metabolite concentrations, local tissue exposure, and the biological effects observed in experimental models and humans.

An important translational consideration is the relationship between systemic piceatannol exposure and the concentrations employed in mechanistic cell-culture studies. Several investigations evaluating adipogenesis, inflammatory signaling, and insulin responsiveness have employed nominal piceatannol concentrations within the micromolar range, including

approximately 5–10 μM, 5–20 μM, and 3–30 μM in selected adipocyte and macrophage models [8]. Although micromolar plasma concentrations have been reported following relatively high oral doses in rats, these findings do not establish that comparable concentrations of unconjugated piceatannol are achieved or sustained in humans receiving the doses investigated in clinical intervention studies. Furthermore, nominal concentrations added to culture media are not directly equivalent to unbound plasma concentrations or intracellular target-site exposure. Extensive conjugation, protein binding, tissue distribution, and metabolite-specific biological activity may further influence the relationship between administered dose and pharmacological effects. Consequently, the exposure–response relevance of the concentrations employed in vitro remains uncertain, highlighting the need for human pharmacokinetic investigations and experimental studies evaluating biologically relevant concentrations of the parent compound and its major metabolites.

Importantly, pharmacokinetic findings should be interpreted according to the experimental model and the specific parameters measured. Evidence of increased plasma exposure, including a higher area under the concentration–time curve (AUC), does not necessarily establish increased concentrations of unconjugated piceatannol or its active metabolites in metabolically relevant tissues. Similarly, improved systemic exposure does not demonstrate molecular target engagement or clinically meaningful metabolic benefits. Most available pharmacokinetic investigations have been conducted in experimental animals, while human data remain limited. Therefore, direct human pharmacokinetic studies incorporating metabolite-specific measurements, exposure–response analyses, and, where feasible, target-tissue assessments are needed to establish the translational relevance of these findings.

3.5. Bioavailability Challenges and Delivery Strategies

Despite its promising biological activities, the clinical translation of piceatannol faces several distinct physicochemical and pharmacokinetic challenges. Limited aqueous solubility may restrict dissolution in gastrointestinal fluids, whereas chemical instability and susceptibility to oxidative degradation may affect the integrity of the parent compound under particular formulation, processing, or environmental conditions. These properties should be distinguished from metabolic stability, which concerns the susceptibility of piceatannol to enzymatic biotransformation, including extensive intestinal and hepatic phase II conjugation. Oral bioavailability represents a separate pharmacokinetic outcome that depends on the combined effects of gastrointestinal absorption and presystemic elimination. Accordingly, formulation strategies intended to improve solubility, chemical stability, oxidative protection, or dissolution should be evaluated according to the specific properties they modify. Improvements in these physicochemical characteristics cannot be assumed to enhance metabolic stability, systemic exposure, target-tissue delivery, or clinical efficacy without appropriate compound-specific pharmacokinetic and pharmacodynamic evidence.

3.5.1. Nanoformulations and Encapsulation Technologies

Nanoformulation and encapsulation technologies have been investigated as potential strategies to address the physicochemical limitations of piceatannol, particularly its limited aqueous solubility, susceptibility to chemical degradation, and formulation-dependent release characteristics. These approaches include nanoemulsions, self-nanoemulsifying drug delivery systems (SNEDDS), emulsomes, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, microencapsulation systems, and cyclodextrin inclusion complexes. Depending on their composition and physicochemical properties, these delivery platforms may improve apparent solubility, drug incorporation, chemical stability, or dissolution and release behavior. However, such improve-

ments should be distinguished from enhanced oral bioavailability, metabolic stability, systemic exposure, target-tissue delivery, or therapeutic efficacy, which require independent experimental confirmation.

Piceatannol-specific investigations remain limited and have primarily evaluated selected formulation characteristics or biological outcomes unrelated to obesity-associated metabolic dysfunction [85–89]. Zhang and Yu [85] investigated a piceatannol nanoemulsion formulation and its in vitro release characteristics, whereas Alhakamy et al. [86] evaluated piceatannol-loaded emulsomes in colon cancer cells. More recently, a piceatannol-loaded SNEDDS was investigated in a diabetic rat wound-healing model [89]. Although these studies provide preliminary evidence supporting the feasibility of selected delivery platforms, they do not collectively establish improved oral pharmacokinetics, enhanced systemic exposure, or superior efficacy against obesity-associated metabolic dysfunction. Moreover, formulation-related improvements observed in vitro or therapeutic responses in non-metabolic disease models should not be interpreted as direct evidence of improved clinical delivery or anti-obesity efficacy.

Cyclodextrin inclusion complexes represent another relevant formulation approach for which compound-specific experimental evidence is available. Studies investigating piceatannol–cyclodextrin interactions have examined physicochemical characteristics and potential improvements in solubilization, while a rat investigation reported enhanced absorption following administration of a piceatannol–α-cyclodextrin complex [52,54]. These findings provide preliminary evidence that cyclodextrin complexation may influence piceatannol absorption under specific experimental conditions. Nevertheless, the available results do not establish corresponding improvements in human systemic exposure, target-tissue concentrations, or clinically meaningful metabolic outcomes. Furthermore, the reported pharmacokinetic effects should not be generalized to other cyclodextrin derivatives or encapsulation platforms without direct comparative investigations.

Additional delivery approaches, including liposomal systems, polymeric nanoparticles, and other lipid-based or encapsulation technologies, have been extensively investigated for resveratrol and various dietary polyphenols [87,88,90,91]. Such studies provide a general formulation-development rationale, particularly regarding improvements in solubility, protection against degradation, and controlled release. However, evidence derived from resveratrol or other polyphenols cannot independently establish equivalent pharmacokinetic or pharmacodynamic benefits for purified piceatannol, given potential differences in physicochemical characteristics, metabolism, formulation interactions, and biological activity. Accordingly, these platforms should be regarded as investigational approaches for piceatannol unless supported by direct compound-specific evidence.

Overall, the principal translational limitation is the insufficient demonstration that improvements in formulation-related properties produce meaningful increases in systemic or target-tissue exposure to biologically active piceatannol species. Future investigations should prioritize standardized comparisons between unformulated and formulated piceatannol, incorporating quantitative oral pharmacokinetic measurements, characterization of unconjugated and conjugated metabolites, tissue-distribution assessments, formulation stability, and relevant pharmacodynamic endpoints. Studies should also determine whether any improvements in exposure translate into reproducible benefits in appropriate experimental models of obesity-associated metabolic dysfunction. Until such evidence becomes available, nanoformulation and encapsulation technologies should be considered promising research approaches rather than established strategies for improving the clinical efficacy of piceatannol.

3.5.2. Future Approaches

Future formulation research should initially prioritize piceatannol-specific characterization of formulation stability, dissolution, oral pharmacokinetics, metabolite exposure, and biodistribution. More complex delivery platforms, including exosome-based carriers, stimulus-responsive nanoparticles, and co-delivery systems, remain speculative in the context of piceatannol and should not be regarded as established or near-term translational opportunities. Their investigation would be justified only after simpler formulations have demonstrated reproducible pharmacokinetic advantages and an acceptable safety profile in appropriate preclinical models.

Increasing understanding of host–microbiome interactions may also inform future investigations into interindividual variability in piceatannol absorption, metabolism, and biological responsiveness. Nevertheless, personalized supplementation strategies and advanced delivery technologies remain exploratory. Their clinical relevance will depend on demonstrating reproducible improvements in systemic exposure, target-tissue availability, molecular target engagement, and clinically meaningful metabolic outcomes. Until these requirements are met, such approaches should be considered future research directions rather than validated strategies for improving piceatannol efficacy.

4. Adipose Tissue Dysfunction and Metabolic Inflammation: Pathophysiological Background

This section briefly outlines the principal adipose tissue abnormalities and inflammatory pathways relevant to the experimental investigation of piceatannol. Particular emphasis is placed on connecting adipocyte hypertrophy, hypoxia, fibrosis, mitochondrial dysfunction, macrophage activation, and inflammatory signaling with molecular targets and biological responses that have been investigated in relation to piceatannol. Importantly, these connections are presented as a pathophysiological framework rather than evidence that piceatannol directly reverses each abnormality. Compound-specific experimental findings, including the strength and limitations of the available mechanistic evidence, are critically evaluated in Section 5 and subsequent sections.

4.1. Adipose Tissue as a Dynamic Endocrine Organ

Adipose tissue integrates lipid storage, endocrine signaling, and immune regulation through interactions among adipocytes, stromal and vascular cells, and resident immune cells [92,93]. Its adipokine profile, particularly adiponectin and leptin signaling, influences insulin sensitivity and inflammatory status. Visceral adipose tissue generally exhibits greater inflammatory and lipolytic activity than subcutaneous depots, contributing to regional differences in cardiometabolic risk [94,95]. These endocrine and metabolic functions provide relevant endpoints for assessing the actions of piceatannol on adipocyte biology.

4.2. Mechanisms Underlying Adipose Tissue Dysfunction

Chronic nutrient excess is associated with multiple, heterogeneous and interconnected alterations in adipose tissue, including adipocyte hypertrophy, impaired vascular adaptation and localized hypoxia, extracellular matrix remodeling and fibrosis, mitochondrial dysfunction, and inflammatory signaling [96,97]. These abnormalities do not necessarily develop in a uniform or obligatory sequence, nor are they invariably present to the same extent in all individuals or adipose tissue depots. Rather, their occurrence, relative contribution, and temporal relationships may vary according to adipose tissue expandability, anatomical location, metabolic status, and individual susceptibility. Furthermore, these processes may develop concurrently, independently, or through reciprocal interactions, collectively contributing to impaired metabolic flexibility and insulin responsiveness. Figure 2

provides a conceptual overview of these interconnected mechanisms rather than depicting a universally established linear progression from adipocyte hypertrophy to insulin resistance. Their relevance to piceatannol lies in the possibility of modifying associated metabolic and inflammatory pathways, rather than reversing all structural features of obesity.

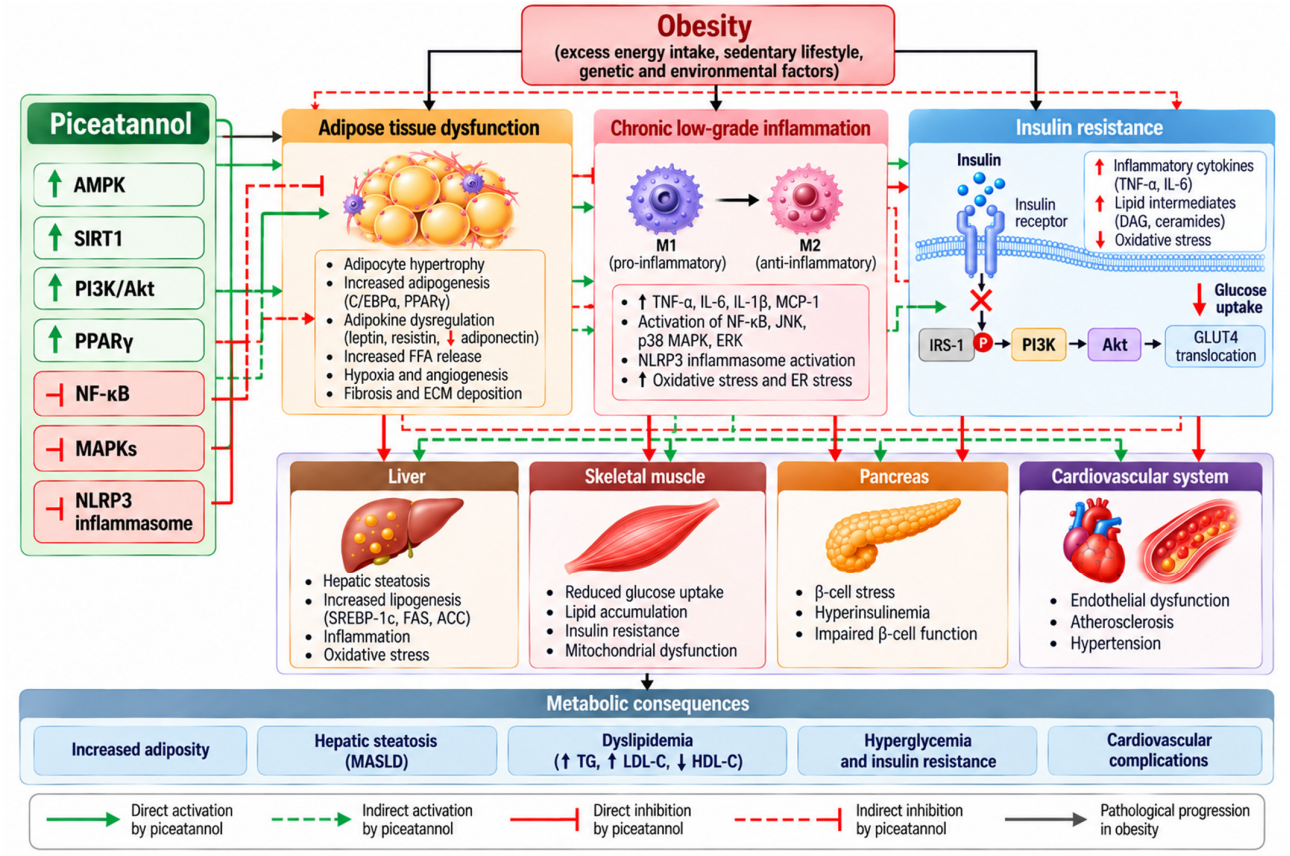


Figure 2. The relationship between adipose tissue dysfunction, inflammation, and insulin resistance.

4.2.1. Adipocyte Hypertrophy

Adipocyte hypertrophy is associated with impaired insulin responsiveness, altered adipokine secretion, and increased oxidative and inflammatory stress [98,99]. As lipid storage capacity becomes constrained, fatty-acid spillover may contribute to ectopic lipid deposition [98,99]. Experimental evaluation of piceatannol therefore focuses in part on adipocyte differentiation, lipid handling, and metabolic signaling, although changes in these endpoints do not necessarily demonstrate reduced adiposity in humans.

4.2.2. Hypoxia

Adipose tissue expansion may outpace vascular adaptation, promoting localized hypoxia and hypoxia-inducible factor-1α (HIF-1α) signaling [100,101]. Sustained hypoxic responses can enhance inflammatory mediator production and extracellular matrix remodeling [100,101]. These pathways provide context for assessing anti-inflammatory effects of piceatannol, but direct effects on adipose hypoxia or HIF-1α should not be inferred without specific experimental evidence. These processes provide a pathophysiological rationale for investigating the potential relevance of piceatannol-associated modulation of NF-κB, MAPK signaling, and oxidative responses in adipose tissue. However, although piceatannol has demonstrated effects on selected inflammatory and oxidative pathways in experimental cellular models, these findings do not establish direct inhibition of HIF-1α

signaling, reversal of adipose tissue hypoxia, or restoration of vascular adaptation. Such effects require specific experimental validation in appropriate adipose tissue models.

4.2.3. Fibrosis

Persistent metabolic stress can promote excessive deposition of collagen and other extracellular matrix components, restricting adipose tissue expandability [102,103]. Fibrosis interacts with hypoxia, oxidative stress, and inflammation and may aggravate ectopic lipid accumulation [102,103]. The involvement of inflammatory and oxidative signaling in extracellular matrix remodeling provides an indirect mechanistic rationale for investigating whether piceatannol-associated modulation of NF-κB, MAPKs, and oxidative responses could influence fibrotic processes. Nevertheless, the available evidence does not establish a direct antifibrotic action of piceatannol in obesity-associated adipose tissue. In particular, suppression of inflammatory mediators should not be interpreted as evidence of reduced collagen deposition, extracellular matrix remodeling, or improved adipose tissue expandability without appropriate functional and histological validation.

4.2.4. Mitochondrial Dysfunction

Mitochondrial impairment in obesity can reduce oxidative capacity and metabolic flexibility while increasing reactive oxygen species (ROS) generation [104,105]. Altered mitochondrial biogenesis and regulators such as PPARγ coactivator-1α (PGC-1α) further connect cellular energy metabolism with oxidative stress [104,105]. These mechanisms provide a rationale for investigating piceatannol-associated AMPK/SIRT1 signaling and oxidative responses; evidence for direct restoration of mitochondrial function must be evaluated by model and endpoint.

4.3. Chronic Low-Grade Inflammation

Obesity-associated adipose inflammation reflects interactions among stressed adipocytes, recruited immune cells, cytokines, and metabolic danger signals [106,107]. Rather than constituting an isolated process, inflammation reinforces oxidative stress and insulin resistance. The relevance to piceatannol is particularly apparent in experimental assessments of cytokine production and NF-κB- and MAPK-associated signaling. Importantly, adipose inflammation may both contribute to and arise from metabolic dysfunction, and its relationship with adipocyte hypertrophy, tissue hypoxia, extracellular matrix remodeling, and insulin resistance is context-dependent and potentially bidirectional rather than uniformly sequential.

4.3.1. Immune Cell Recruitment and Macrophage Polarization

Obesity promotes monocyte recruitment through chemokines such as MCP-1/CCL2 and the accumulation of inflammatory macrophage populations in adipose tissue [108,109]. Although macrophage activation has traditionally been described using pro-inflammatory M1-like and alternatively activated M2-like phenotypes, this binary framework represents a simplified experimental classification and does not adequately capture the phenotypic, transcriptional, metabolic, and functional heterogeneity of human adipose-tissue macrophages. In particular, macrophage populations may exhibit overlapping activation signatures and context-dependent functional states that vary according to adipose tissue depot, metabolic conditions, and local microenvironmental signals. Accordingly, M1-like/M2-like terminology should be regarded as a descriptive approximation rather than evidence of two discrete or mutually exclusive macrophage populations. Within this framework, piceatannol-associated modulation of NF-κB and MAPK signaling, inflammatory mediator production, and adipocyte–macrophage interactions represents a relevant mechanistic area

for investigation. Experimental studies involving macrophages or adipocyte–macrophage coculture systems may provide evidence of altered inflammatory signaling and cellular communication; however, these findings should not automatically be interpreted as demonstrating macrophage repolarization or comprehensive remodeling of adipose tissue immune populations. Establishing such effects requires appropriate functional and phenotypic characterization, ideally supported by in vivo investigations of adipose tissue immune-cell composition and activation states.

4.3.2. Dysregulated Cytokine and Adipokine Secretion

Adipose tissue dysfunction is associated with increased TNF-α, IL-1β, IL-6, and MCP-1 signaling and reduced adiponectin activity [107,110]. These changes contribute to impaired insulin signaling and reduced AMPK-associated metabolic regulation [107,110]. Accordingly, inflammatory mediators and adiponectin-related pathways are pertinent to the mechanistic evaluation of piceatannol, although changes in isolated biomarkers cannot establish systemic metabolic efficacy.

4.3.3. Inflammatory Signaling Pathways

NF-κB coordinates transcription of inflammatory mediators, including TNF-α, IL-6, IL-1β, MCP-1, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) [111]. JNK, p38 MAPK, ERK, and the NLRP3 inflammasome also participate in obesity-associated inflammatory signaling and can interfere with insulin receptor substrate (IRS) function [107,110,111]. These pathways are particularly relevant to piceatannol because cellular investigations examine its association with inflammatory pathway modulation and insulin-related signaling. However, pathway-level changes should be interpreted in relation to experimental concentrations, model specificity, and the absence of definitive clinical target validation.

In addition to these downstream inflammatory mediators, spleen tyrosine kinase (Syk), a non-receptor protein tyrosine kinase, represents an important upstream regulator of selected immune-receptor-mediated signaling pathways [112–114]. Following activation of receptors containing immunoreceptor tyrosine-based activation motifs (ITAMs), Syk participates in the transmission of intracellular signals that regulate immune-cell activation and inflammatory responses. Depending on the receptor and cellular context, Syk-associated signaling may influence downstream pathways involving NF-κB, MAPKs, and other inflammatory mediators [112–114]. Syk-dependent signaling has also been implicated in the regulation of NLRP3 inflammasome activation in selected experimental contexts, although this relationship is stimulus- and cell-type-dependent and should not be considered universal. Piceatannol has historically been characterized as a pharmacological inhibitor of Syk, suggesting a potential upstream mechanism through which it may modulate inflammatory signaling [112–114]. Nevertheless, piceatannol is not a highly selective Syk inhibitor, and direct evidence demonstrating that its effects on NF-κB, MAPKs, or NLRP3 activation in obesity-associated adipose tissue are mediated specifically through Syk inhibition remains insufficient. Further studies employing Syk-specific genetic or pharmacological interventions are required to establish the contribution of this pathway to the anti-inflammatory and metabolic actions of piceatannol [112–114].

5. Mechanistic Effects of Piceatannol on Adipocyte Biology: Evidence from Cellular Studies

Direct cellular studies provide the mechanistic foundation for understanding how piceatannol may modulate adipose tissue biology before these effects are evaluated in experimental animals or humans. Representative mechanistic studies are summarized in Table 1.

Although the available literature remains relatively limited, in vitro investigations demonstrate that piceatannol may influence several key biological processes involved in adipocyte differentiation, lipid metabolism, inflammatory signaling, and insulin responsiveness. To maintain a clear evidence hierarchy, this section includes only mechanistic studies performed in adipocytes, preadipocytes, adipose-derived stem cells, or adipocyte–macrophage coculture systems. Findings obtained in other cell types, although potentially relevant for obesity-related pathophysiology, are not discussed here because they do not constitute direct evidence of piceatannol action in adipose tissue. Furthermore, this section focuses primarily on studies investigating purified piceatannol, while selected investigations employing piceatannol-rich botanical extracts are included as complementary, preparation-specific evidence when relevant to the mechanistic discussion. Importantly, findings obtained with such extracts are distinguished from those involving purified piceatannol and are not attributed exclusively to the isolated compound.

5.1. Modulation of Adipocyte Differentiation and Adipogenesis: Experimental Evidence and Metabolic Implications

Inhibition of adipocyte differentiation is among the more frequently reported cellular effects of purified piceatannol and may represent an important component of its experimental mechanistic profile. Studies performed in murine and human adipocyte precursor models have reported interference with early adipogenic differentiation, accompanied by reduced lipid accumulation and changes in adipogenic marker expression [115–117]. These findings provide potential functional evidence of anti-adipogenic activity under defined in vitro conditions, but do not establish that piceatannol prevents adipose tissue expansion or improves metabolic health in vivo.

The seminal study by Kwon et al. (2012) provided the first detailed mechanistic evidence that purified piceatannol may inhibit adipogenesis in 3T3-L1 preadipocytes [115]. Piceatannol reduced adipocyte differentiation in a concentration-dependent manner without substantially affecting cell viability, indicating that its anti-adipogenic activity could not be explained by nonspecific cytotoxicity. Notably, the inhibitory effect was greatest when piceatannol was administered during the early phase of differentiation, whereas treatment during later stages produced considerably smaller effects [115]. This temporal dependence demonstrated that piceatannol may primarily target the initial molecular events governing adipocyte commitment rather than the maintenance of the mature adipocyte phenotype. Consistent with this mechanism, treated cells exhibited markedly reduced intracellular lipid accumulation together with decreased expression of the master adipogenic transcription factors CCAAT/enhancer-binding protein β (C/EBPβ), C/EBPα, and PPARγ, all of which are indispensable for terminal adipocyte differentiation [115].

A major mechanistic contribution of Kwon et al. (2012) was the demonstration that piceatannol could suppress mitotic clonal expansion (MCE), a transient proliferative phase that occurs immediately after adipogenic induction and is required for terminal differentiation of 3T3-L1 preadipocytes [115]. Piceatannol delayed progression through the cell cycle, reducing entry into the G_2/M phase and limiting the increase in cell number that normally accompanies adipogenic commitment. This effect was associated with attenuation of insulin receptor-dependent proliferative signaling, including reduced phosphorylation of the insulin receptor, insulin receptor substrate-1 (IRS-1), phosphatidylinositol 3-kinase (PI3K), and Akt, together with moderate suppression of extracellular signal-regulated kinase 1/2 (ERK1/2) activation [115]. Importantly, this study did not directly evaluate the expression or activity of individual cyclins, cyclin-dependent kinases (CDKs), p21, p27, mammalian target of rapamycin (mTOR), or other cell-cycle regulatory proteins [115]. Therefore, current evidence supports the conclusion that piceatannol inhibits MCE through

delayed cell-cycle progression and suppression of insulin receptor-mediated proliferative signaling, whereas involvement of specific downstream cell-cycle regulators remains to be experimentally confirmed.

Subsequent investigations extended these observations to human adipocyte precursor cells, indicating that the anti-adipogenic activity of piceatannol is not restricted to murine experimental models. Carpéné et al. (2018) demonstrated that piceatannol inhibited adipogenic differentiation of human adipose-derived mesenchymal stem cells, resulting in reduced neutral lipid accumulation and impaired development of the metabolic phenotype characteristic of mature adipocytes [116]. Differentiating cells also exhibited lower expression of PPARγ, fatty acid synthase (FASN), glucose transporter type 4 (GLUT4), and reduced glucose uptake, reflecting suppression of the adipogenic program rather than induction of pathological insulin resistance. Although mitotic clonal expansion and cell-cycle progression were not directly investigated, these findings independently indicated that piceatannol may suppress adipocyte differentiation in human precursor cells through inhibition of adipogenic maturation [116].

Comparable findings were subsequently reported by Park et al. (2021) using human visceral adipose-derived stem cells [117]. Piceatannol reduced intracellular lipid accumulation and downregulated the expression of key adipogenic markers, including PPARγ, C/EBPα, and fatty acid-binding protein 4 (FABP4) [117]. Under the experimental conditions investigated, Park et al. (2021) reported greater inhibition of selected adipogenic endpoints by piceatannol than by resveratrol in human visceral adipose-derived stem cells [117]. This direct comparison provides evidence of an endpoint-specific difference in the investigated cellular model but does not establish greater anti-obesity efficacy, improved adipose-tissue function, or superior therapeutic activity in vivo.

Taken together, the available cellular studies provide convergent experimental evidence that purified piceatannol can inhibit adipogenic differentiation in selected murine and human precursor-cell models. However, the underlying mechanistic evidence differs between these experimental systems. Specifically, inhibition of mitotic clonal expansion (MCE), delayed cell-cycle progression, and attenuation of insulin receptor/IRS-1/PI3K/Akt-associated signaling during early adipogenesis were demonstrated in murine 3T3-L1 preadipocytes by Kwon et al. (2012) [115]. In contrast, studies involving human adipose-derived mesenchymal stem cells and human visceral adipose-derived stem cells primarily documented reduced intracellular lipid accumulation and altered expression of adipogenic or metabolic markers, including PPARγ, C/EBPα, FASN, GLUT4, and FABP4 [116,117]. These human studies did not directly establish inhibition of MCE or demonstrate that the cell-cycle mechanism identified in 3T3-L1 cells operates in human adipose progenitors. Accordingly, the available findings should be interpreted as model-specific, pathway-associated, and functional cellular observations rather than definitive evidence of shared molecular mechanisms across species or of corresponding effects in intact adipose tissue. The involvement of downstream cell-cycle regulators, including cyclins, CDKs, p21, p27, and mTOR, remains insufficiently investigated and should currently be regarded as hypothetical rather than established mechanisms of piceatannol action.

Importantly, suppression of adipogenic differentiation and intracellular lipid accumulation should not be equated with improvement in adipose-tissue function. Physiological adipogenesis contributes to adipose-tissue expandability and the capacity for metabolically appropriate lipid storage, whereas impaired adipocyte recruitment may contribute to adipocyte hypertrophy and ectopic lipid deposition under conditions of sustained energy excess. Therefore, the functional significance of piceatannol-induced inhibition of adipogenesis remains context-dependent and requires direct investigation in intact adipose tissue.

5.2. Context-Dependent Regulation of Insulin Signaling

The available cellular evidence indicates that the effects of purified piceatannol on insulin signaling are highly dependent on the biological context in which they are examined. At first glance, published studies appear to report opposing effects, with piceatannol suppressing insulin signaling during adipocyte differentiation while preserving insulin responsiveness in mature adipocytes exposed to inflammatory stress. However, these findings are not contradictory because insulin signaling serves distinct physiological functions during adipogenesis and in fully differentiated adipocytes. Consequently, the biological effects of piceatannol should be interpreted according to the developmental stage of the adipocyte and the presence or absence of inflammatory stimuli rather than as a simple activation or inhibition of insulin signaling.

In the murine 3T3-L1 preadipocyte differentiation model, insulin-dependent signaling contributes to the early adipogenic program, including mitotic clonal expansion, a proliferative process that should not be assumed to occur through an equivalent mechanism in human adipose progenitors. Kwon et al. (2012) demonstrated that piceatannol inhibited insulin receptor kinase activity and attenuated phosphorylation of the insulin receptor, IRS-1, PI3K, and Akt in differentiating 3T3-L1 preadipocytes [115]. This suppression of insulin receptor-dependent signaling impaired mitotic clonal expansion and reduced activation of adipogenic transcription factors, thereby contributing directly to inhibition of adipocyte differentiation. In this experimental setting, attenuation of insulin signaling represents an anti-adipogenic mechanism rather than an impairment of insulin sensitivity [115].

Consistent with these observations, Carpéné et al. (2018) reported that piceatannol reduced GLUT4 abundance and glucose uptake in human adipose-derived mesenchymal stem cells undergoing adipogenic differentiation [116]. Because expression of GLUT4 normally increases as precursor cells differentiate into mature adipocytes, these findings primarily reflect suppression of adipogenic maturation and reduced acquisition of the metabolic phenotype characteristic of mature adipocytes [116]. Accordingly, decreased glucose uptake in differentiating cells should not be interpreted as evidence of pathological insulin resistance but rather as a consequence of inhibited adipocyte development.

In contrast, the biological role of insulin signaling differs substantially in mature adipocytes, where it primarily regulates glucose uptake and maintains metabolic homeostasis. Under inflammatory conditions, pro-inflammatory cytokines such as TNF-α impair insulin signaling and contribute to the development of adipocyte insulin resistance. Using differentiated 3T3-L1 adipocytes challenged with TNF-α, Li et al. (2017) demonstrated that piceatannol attenuated inflammatory signaling and partially restored insulin-stimulated glucose uptake [118]. These findings indicate that, in mature adipocytes, piceatannol may preserve insulin responsiveness indirectly through suppression of inflammation rather than by directly stimulating the insulin signaling cascade itself [118]. The insulin-sensitizing effects observed in this model therefore appear to be secondary to attenuation of inflammatory stress, which is a major contributor to obesity-associated insulin resistance.

Collectively, the available evidence demonstrates that piceatannol does not exert a uniform stimulatory or inhibitory effect on insulin signaling. Instead, its actions are determined by the physiological context in which insulin signaling operates. During adipocyte differentiation, suppression of insulin receptor/IRS-1/PI3K/Akt signaling contributes to inhibition of mitotic clonal expansion and adipogenesis. Conversely, in mature adipocytes exposed to inflammatory stress, attenuation of inflammatory signaling preserves insulin responsiveness and glucose metabolism. These observations indicate that piceatannol may function as a context-dependent modulator of insulin action, with its biological effects

reflecting the distinct physiological roles of insulin signaling during adipocyte development and metabolic regulation.

5.3. Regulation of Adipocyte Inflammation and Adipocyte–Macrophage Crosstalk

A limited number of cellular investigations suggest that purified piceatannol can attenuate inflammatory responses in cultured adipocytes and macrophages and influence inflammatory communication between these cell populations under experimentally induced conditions. However, these observations do not establish equivalent effects within intact adipose tissue or demonstrate modulation of adipose-tissue inflammation in vivo. These mechanisms have been investigated primarily using adipocyte–macrophage coculture systems and cytokine-stimulated adipocytes.

The first direct evidence was provided by Yamamoto et al. (2017) using experimental models that reproduced the inflammatory interaction between adipocytes and macrophages [119]. In RAW264.7 macrophages stimulated either with lipopolysaccharide or with conditioned medium derived from hypertrophied 3T3-L1 adipocytes, piceatannol significantly reduced the expression of inducible NOS (iNOS), TNF-α, IL-6, accompanied by decreased nitric oxide production and reduced secretion of TNF-α and IL-6 [119]. These findings demonstrate that piceatannol may directly suppress macrophage inflammatory activation in response to obesity-associated adipocyte-derived stimuli, thereby interrupting one of the principal mechanisms responsible for amplification of adipose tissue inflammation.

Beyond its effects on macrophages, Yamamoto et al. (2017) further investigated the ability of piceatannol to attenuate selected molecular responses of adipocytes to macrophage-derived inflammatory mediators [119]. In adipocytes exposed to conditioned medium from activated macrophages, inflammatory stress markedly suppressed isoproterenol-induced uncoupling protein 1 (UCP1) mRNA expression, whereas treatment with piceatannol partially restored UCP1 mRNA levels [119]. Importantly, this observation represents a transcriptional response and should not be interpreted as evidence of restored UCP1 protein abundance, mitochondrial uncoupling, thermogenic activity, cellular respiration, mitochondrial function, or whole-body energy expenditure, none of which were directly established by the reported UCP1 mRNA measurement. Demonstrating functional thermogenic recovery would require complementary assessments, including UCP1 protein expression and appropriate measurements of mitochondrial oxygen consumption, proton leak, and thermogenic activity. Accordingly, these findings suggest that piceatannol may attenuate inflammation-associated suppression of a thermogenesis-related gene-expression marker, rather than demonstrating restoration of adipocyte thermogenic capacity or mitochondrial function. The study also showed that several piceatannol metabolites retained anti-inflammatory activity, although the parent compound generally produced more efficient biological effects than its metabolites [119].

Li et al. (2017) further demonstrated that attenuation of inflammatory signaling by piceatannol was accompanied by partial restoration of insulin-stimulated glucose uptake in TNF-α-challenged mature adipocytes, illustrating the functional relationship between inflammatory regulation and insulin responsiveness [118]. Under these inflammatory conditions, piceatannol attenuated inflammatory signaling and partially restored insulin-stimulated glucose uptake, indicating that suppression of inflammatory pathways was accompanied by preservation of adipocyte insulin responsiveness [118]. These observations provide direct evidence that piceatannol may not only inhibit inflammatory activation but also alleviate one of its principal metabolic consequences, namely inflammation-induced impairment of insulin action in mature adipocytes.

Complementary, preparation-specific evidence concerning the modulation of adipocyte–macrophage inflammatory interactions was reported by Chusongdam et al. (2024), who

investigated a piceatannol-rich passion fruit seed extract in an adipocyte–macrophage coculture model [120]. The extract reduced production of inflammatory mediators and suppressed activation of the p38 MAPK and NF-κB signaling pathways, two central regulators of obesity-associated inflammation [120]. These findings are consistent with the anti-inflammatory actions reported for purified piceatannol. However, because passion fruit seed extract contains additional bioactive constituents, including scirpusin B and other phenolic compounds, the observed effects cannot be attributed exclusively to piceatannol. Consequently, this study should be regarded as supportive rather than definitive evidence for the anti-inflammatory activity of purified piceatannol. Furthermore, the phytochemical complexity of the extract prevents definitive identification of the constituent or combination of constituents responsible for the observed inhibition of p38 MAPK and NF-κB signaling. Direct comparisons between purified piceatannol, the complete extract, and appropriately characterized extract fractions would be required to establish the relative contribution of piceatannol and determine whether additional botanical constituents modify its anti-inflammatory activity [120].

An additional molecular mechanism potentially contributing to the anti-inflammatory activity of piceatannol involves inhibition of Syk, a proximal signaling enzyme involved in immune-receptor-mediated activation [112–114]. Early biochemical and cellular investigations identified piceatannol as an inhibitor of protein tyrosine kinases, while subsequent experiments demonstrated preferential inhibition of Syk relative to Lyn in selected mast-cell models. Inhibition of Syk activation was associated with attenuation of receptor-mediated downstream signaling and cellular responses. These findings suggest that piceatannol may interfere with inflammatory signaling at an upstream regulatory level rather than exclusively modifying downstream transcription factors and inflammatory mediators [112–114]. However, piceatannol is not a highly selective Syk inhibitor, and its effects on NF-κB and other signaling pathways cannot necessarily be attributed to Syk inhibition. Indeed, Syk-independent inhibition of NF-κB activation has been demonstrated in other cellular systems. Within the context of obesity-associated metabolic dysfunction, Syk inhibition therefore represents a plausible additional mechanism through which piceatannol might influence macrophage activation and adipocyte–macrophage inflammatory communication. Nevertheless, direct evidence establishing Syk inhibition as a causal mediator of piceatannol's effects in adipose tissue remains limited. Further studies incorporating Syk-specific genetic or pharmacological interventions are required to determine its contribution to the anti-inflammatory and metabolic actions of piceatannol [112–114].

Collectively, the available cellular evidence indicates that purified piceatannol may attenuate inflammatory responses in selected adipocyte and macrophage models, whereas findings obtained with piceatannol-rich botanical extracts provide complementary, preparation-specific evidence that cannot be attributed exclusively to the isolated compound. In selected cellular models, piceatannol attenuated inflammatory responses associated with communication between adipocytes and macrophages, suggesting a potentially relevant mechanism for obesity-associated inflammation. Nevertheless, whether comparable effects occur within intact adipose tissue, alter macrophage recruitment or phenotype, or contribute to improvements in metabolic function in vivo remains unknown. Moreover, the current evidence remains limited to a small number of cellular models, and several mechanisms frequently proposed in the literature—including induction of macrophage polarization toward an M2-like phenotype, modulation of inflammasome activation, and regulation of adipose tissue immune-cell composition—have not yet been convincingly demonstrated in adipocyte-specific experimental systems. Accordingly, these mechanisms should presently be regarded as hypothetical rather than established actions of piceatannol in adipose tissue.

5.4. Regulation of Adipocyte Lipid Metabolism

Piceatannol has been investigated for its effects on adipocyte lipid metabolism, although its actions must be distinguished according to adipocyte differentiation stage and the specific metabolic process assessed. In differentiating preadipocytes, reduced intracellular lipid accumulation has been observed in association with inhibition of adipogenic differentiation [115,116]. However, this finding does not establish direct suppression of triglyceride synthesis or stimulation of triglyceride hydrolysis in mature adipocytes. In contrast, Kwon et al. (2022) demonstrated that piceatannol antagonized lipolysis in differentiated adipocytes through autophagy–lysosome-dependent degradation of lipolytic proteins, including adipose triglyceride lipase (ATGL), comparative gene identification-58 (CGI-58), and perilipin 1 (PLIN1) [121]. Therefore, the available evidence supports distinct, experimentally context-dependent effects on adipocyte lipid accumulation and lipolysis rather than a generalized lipid-mobilizing action of piceatannol.

Piceatannol has been reported to reduce intracellular lipid accumulation during adipocyte differentiation, accompanied by decreased expression of adipogenic transcription factors and selected lipid-metabolism-associated proteins [115,116]. These observations should be interpreted primarily within the context of impaired adipogenic maturation, rather than as definitive evidence of direct inhibition of de novo lipogenesis or increased lipolytic activity in mature adipocytes. Because adipogenic differentiation, triglyceride synthesis, lipid-droplet formation, and triglyceride hydrolysis represent distinct processes, changes in intracellular lipid content alone cannot identify the metabolic pathway responsible. Direct measurements of triglyceride synthesis, fatty-acid incorporation, glycerol and nonesterified fatty-acid release, and relevant enzyme activity would be required to distinguish these mechanisms. Furthermore, reduced lipid accumulation during differentiation should not automatically be regarded as metabolically beneficial, because physiological adipogenesis contributes to adipose-tissue expandability and appropriate lipid storage.

In contrast to suggestions that piceatannol stimulates lipid mobilization, Kwon et al. (2022) demonstrated an inhibitory effect on lipolysis in differentiated adipocytes [121]. Specifically, piceatannol promoted autophagy–lysosome-dependent degradation of key lipolytic proteins, including ATGL, CGI-58, and PLIN1, accompanied by reductions in glycerol and free fatty-acid release. These findings provide direct experimental evidence that piceatannol can suppress triglyceride hydrolysis under the conditions investigated. Importantly, this response is mechanistically distinct from the reduction in lipid accumulation observed during preadipocyte differentiation. Conversely, Arisawa et al. (2023) reported increased lipolysis-associated responses in ovariectomized female mice receiving dietary piceatannol [122]. These observations should not be considered equivalent or directly contradictory without accounting for differences in experimental model, hormonal status, treatment duration, biological compartment, and lipolysis assessment methods. The available findings therefore indicate context-dependent effects rather than consistent stimulation or suppression of lipolysis across experimental systems.

Collectively, the available evidence indicates that piceatannol can influence adipocyte lipid-related processes, but reduced lipid accumulation during adipogenic differentiation, inhibition of triglyceride hydrolysis in mature adipocytes, and changes in lipolysis-associated responses in animal models must be interpreted as distinct experimental findings. In particular, the mechanistic observations of Kwon et al. (2022) [121] demonstrate suppression rather than stimulation of lipolysis in the investigated adipocyte systems. Although these findings suggest that piceatannol may influence lipid handling under different metabolic conditions, they do not establish a uniform direction of effect or demonstrate improved adipose-tissue lipid-buffering capacity in vivo. Further studies employing direct measure-

ments of triglyceride turnover, fatty-acid flux, lipolytic enzyme activity, and tissue-specific metabolic responses are required to clarify the physiological relevance of these observations.

5.5. Integrated Interpretation and Critical Appraisal of the Cellular Evidence

Collectively, the available cellular evidence demonstrates that purified piceatannol may exert pleiotropic actions on adipocyte biology by modulating several interconnected processes involved in adipose tissue dysfunction. Despite the relatively limited number of mechanistic studies, the findings could consistently support four principal biological activities: inhibition of adipocyte differentiation, regulation of lipid metabolism, attenuation of adipocyte-associated inflammatory signaling and adipocyte–macrophage crosstalk, and context-dependent modulation of insulin signaling. Importantly, the reported effects on lipid metabolism should not be interpreted as uniformly lipolytic. Reduced intracellular lipid accumulation during adipocyte differentiation is mechanistically distinct from direct regulation of triglyceride hydrolysis in mature adipocytes, and Kwon et al. (2022) demonstrated suppression of lipolysis through degradation of key lipolytic proteins [121]. Although these cellular responses involve interconnected biological pathways, their combined effects on adipose-tissue homeostasis remain uncertain. In particular, suppression of adipocyte differentiation and lipid accumulation should not be assumed to preserve adipose-tissue function, because physiological adipogenesis contributes to adipose expandability and appropriate lipid storage. Whether piceatannol favorably modulates these processes depends on the metabolic context and requires direct evaluation in vivo.

Among the cellular effects of piceatannol, inhibition of adipogenic differentiation is relatively well documented. However, the underlying mechanistic evidence differs between experimental models. Kwon et al. (2012) demonstrated inhibition of mitotic clonal expansion and attenuation of insulin receptor/IRS-1/PI3K/Akt-associated signaling during early adipogenesis in murine 3T3-L1 preadipocytes [115]. In contrast, investigations involving human adipose-derived stem cells primarily reported reduced lipid accumulation and altered expression of adipogenic markers without directly establishing the same cell-cycle-related mechanism [116,117]. These findings support anti-adipogenic activity in selected cellular models but do not demonstrate identical molecular mechanisms across species or establish beneficial effects on adipose-tissue function in vivo.

An important emerging concept from the available literature is that the major mechanisms influenced by piceatannol may be mechanistically interconnected rather than biologically independent. However, the metabolic consequences of inhibiting adipogenesis are potentially bidirectional. Under certain experimental conditions, suppression of excessive adipocyte differentiation and lipid accumulation may accompany favorable changes in selected metabolic or inflammatory endpoints. Conversely, sustained inhibition of adipocyte recruitment, particularly in subcutaneous adipose tissue, could theoretically restrict adipose-tissue expandability, increase the lipid burden of existing adipocytes, and promote fatty-acid spillover and ectopic lipid deposition. Such adverse consequences have not been directly demonstrated following piceatannol administration and should therefore be considered plausible physiological concerns rather than established effects. Attenuation of inflammatory signaling and modulation of lipid metabolism may represent additional biological activities of piceatannol, but whether these responses collectively preserve adipose-tissue homeostasis remains to be established through integrated in vivo investigations assessing adipocyte turnover, depot-specific lipid storage, and systemic metabolic outcomes.

Despite these promising mechanistic findings, the current evidence base remains relatively limited. Most studies have employed immortalized murine 3T3-L1 cells, whereas considerably fewer investigations have used primary human adipocytes or adipose-derived stem cells. Moreover, several mechanisms frequently proposed in the literature—including

regulation of mTOR, cyclins, cyclin-dependent kinases, p21, p27, Nrf2, PGC-1α, inflammasome activation, mitochondrial biogenesis, macrophage polarization, and adipose tissue remodeling—have not yet been directly demonstrated in adipocyte-specific experimental systems. These pathways should therefore be regarded as biologically plausible but presently unconfirmed mechanisms of piceatannol action in adipose tissue.

The translational significance of the available cellular evidence should also be interpreted cautiously. Most mechanistic studies have employed unconjugated piceatannol at micromolar concentrations that may exceed physiologically achievable circulating concentrations following oral administration. Furthermore, extensive phase II metabolism results predominantly in glucuronidated, sulfated, and methylated metabolites, whereas unconjugated piceatannol represents only a minor circulating fraction. Consequently, the relative biological contributions of the parent compound and its metabolites remain largely unresolved and constitute an important limitation when extrapolating cellular findings to in vivo physiology.

Future studies should therefore evaluate both unconjugated piceatannol and its major circulating metabolites at physiologically relevant concentrations using advanced experimental models that more closely reproduce human adipose tissue biology, including primary adipocytes from different fat depots, three-dimensional adipose organoids, and adipocyte–immune cell coculture systems. Integration of these mechanistic models with comprehensive pharmacokinetic, biodistribution, metabolite profiling, and pharmacodynamic studies will be essential for defining tissue exposure, identifying the biologically active molecular species, and bridging the current gap between mechanistic cellular studies, experimental animal models, and human clinical investigations. The principal mechanistic findings from representative in vitro investigations are summarized in Table 1.

Table 1. Representative in vitro mechanistic studies investigating the effects of piceatannol on adipogenesis, adipocyte metabolism, inflammation, insulin resistance, and lipolysis *#.

Study	Cellular Model	Intervention	Principal Mechanistic Findings	Strengths and Limitations
Kwon et al. (2012) [115]	3T3-L1 preadipocytes	Purified piceatannol (0–50 μM)	Inhibited early adipogenesis by suppressing insulin receptor/IRS-1/PI3K/Akt signaling, thereby reducing C/EBPβ, C/EBPα, PPARγ, and lipid accumulation.	Landmark mechanistic study; limited to murine in vitro evidence.
Carpéné et al. (2018) [116]	Human adipose-derived mesenchymal stem cells	Purified piceatannol (mainly 50 and 100 μM)	Inhibited adipocyte differentiation by downregulating PPARγ, FASN, and GLUT4, reducing lipid accumulation, producing greater inhibition of adipogenesis than resveratrol.	Human cell model supports translational relevance.
Park et al. (2021) [117]	Human visceral adipose-derived stem cells	Purified piceatannol (5–20 μM)	Downregulated PPARγ, C/EBPα, and FABP4, producing greater inhibition of adipogenesis than resveratrol.	Human visceral adipocyte model; endpoint-specific differences do not establish superior anti-obesity efficacy or therapeutic activity in vivo
Li et al. (2017) [118]	Differentiated 3T3-L1 adipocytes and adipocyte–macrophage coculture	Purified piceatannol (5 and 10 μM, mainly 10 μM)	Suppressed NF-κB/JNK signaling, reduced TNF-α, IL-6 and MCP-1, and improved insulin-stimulated glucose uptake.	Demonstrates protection against inflammation-induced insulin resistance in vitro.

Table 1. *Cont.*

Study	Cellular Model	Intervention	Principal Mechanistic Findings	Strengths and Limitations
Yamamoto et al. (2017) [119]	RAW264.7 macrophages, hypertrophied 3T3-L1 adipocyte-conditioned medium, and C3H10T1/2 adipocytes	Purified piceatannol (3–30 μM; mainly 30 μM)	Attenuated adipocyte–macrophage inflammatory crosstalk by reducing iNOS, NO, TNF-α, and IL-6 production while partially restoring UCP1 mRNA expression.	First evidence for anti-inflammatory crosstalk modulation; no in vivo validation.
Chusongdam et al. (2024) [120]	3T3-L1 adipocyte–RAW264.7 macrophage coculture	Piceatannol-rich passion fruit seed extract (10, 50, and 100 μg/mL)	Suppressed p38 MAPK/NF-κB signaling, reducing oxidative stress, ROS, TNF-α, IL-1β, MMP-2, IL-6, and MCP-1. MCP and adipocyte–macrophage inflammatory crosstalk.	Preparation-specific anti-inflammatory effects; the contribution of purified piceatannol cannot be isolated from that of other phytochemical constituents without direct comparative experiments.
Kwon et al. (2022) [121]	Differentiated 3T3-L1 adipocytes, murine brown adipocytes, isolated white adipose tissue	Purified piceatannol (0–50 μM in vitro	Suppressed lipolysis through autophagy-mediated degradation of ATGL, CGI-58, and PLIN1, reducing glycerol and fatty acid release.	First study identifying autophagy-dependent regulation of lipolysis.

* **Abbreviations:** Akt, protein kinase B; ATGL, adipose triglyceride lipase; C/EBPα, CCAAT/enhancer-binding protein alpha; C/EBPβ, CCAAT/enhancer-binding protein beta; CGI-58, comparative gene identification-58 (also known as ABHD5); FABP4, fatty acid-binding protein 4; FASN, fatty acid synthase; GLUT4, glucose transporter type 4; IL-1β, interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP-2, matrix metalloproteinase-2; NF-κB, nuclear factor kappa B; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; PLIN1, perilipin 1; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; UCP1, uncoupling protein 1. # **Notes:** The table summarizes representative in vitro studies investigating the effects of piceatannol on adipocyte biology and metabolic signaling. Findings from piceatannol-rich extracts cannot be attributed exclusively to piceatannol. Reduced lipid accumulation during adipogenesis should not be equated with increased lipolysis, as Kwon et al. (2022) [121] demonstrated suppression of lipolysis in mature adipocytes. Comparisons with resveratrol are limited to the specific experimental conditions examined. Changes in molecular signaling do not necessarily establish causal mechanisms, and cellular findings cannot be directly extrapolated to in vivo efficacy or clinical benefits.

6. Evidence from Experimental Animal Models of Obesity and Metabolic Dysfunction

Animal models provide an intermediate level of evidence between cellular experiments (Section 5) and human investigations by allowing assessment of adiposity, glucose regulation, inflammation, and lipid metabolism in intact physiological systems. The following subsections distinguish these outcome domains while identifying where piceatannol-associated molecular changes have, and have not, been linked to functional metabolic responses. Importantly, demonstration of a physiological response in an animal model should not be interpreted as validation of the underlying molecular mechanism unless the proposed pathway has been directly manipulated or its causal contribution otherwise established. Similarly, beneficial findings from individual animal studies provide model-specific functional evidence rather than proof of reproducible preclinical efficacy or clinical effectiveness.

The in vivo literature remains limited and includes diet-induced, genetically determined, and ovariectomy-associated metabolic dysfunction, with variation in compound preparation, administration route, dose, and treatment duration. Results should therefore be interpreted by outcome and model rather than as uniform evidence of efficacy. Table 2 summarizes the principal experimental findings.

Table 2. Summary of the effects of piceatannol in experimental animal models of obesity and metabolic dysfunction across major metabolic outcomes *#.

Study	Animal Model	Dose, Route of Administration, and Duration	Principal Metabolic Effects	Major Conclusion
Kwon et al. (2022) [121]	Diet-induced obese C57BL/6 mice	10 mg/kg/day Piceatannol, intraperitoneal injection, 2 weeks	↓ Pathological lipolysis; ↓ circulating FFAs; improved adipose tissue homeostasis	Piceatannol exhibited anti-lipolytic activity under the investigated experimental conditions, rather than enhanced lipid mobilization.
Tung et al. (2016) [77]	HFD-fed C57BL/6 mice	0.1% or 0.25% (*w*/*w*) Piceatannol in diet; dietary administration, 18 weeks	↓ Body weight gain; ↓ visceral adiposity; ↓ adipocyte hypertrophy; ↓ fasting blood glucose; ↓ serum cholesterol, LDL-C, triglycerides; ↓ hepatic steatosis	Physiological evidence supporting anti-obesity, antihyperglycemic, and lipid-lowering activities.
Arisawa et al. (2023) [122]	Ovariectomized C57BL/6J mice	0.25% (*w*/*w*) Piceatannol in HFD, dietary administration, 12 weeks	↓ Body weight gain; ↓ visceral adiposity; ↓ serum total cholesterol; ↑ lipolysis; ↑ thermogenic signaling	Supports piceatannol as a promising intervention for postmenopausal obesity.
Sun et al. (2025) [123]	HFD-induced obese C57BL/6J mice	HFD + 12.84 mg/kg body weight/day Piceatannol, intraperitoneal injection, 14 weeks	Reduced fasting glucose and HOMA-IR; improved glucose tolerance; changes in adiposity, inflammatory markers, and hepatic lipid metabolism	Piceatannol was more effective in improving glucose metabolism disorders compared with resveratrol.
Uchida-Maruki et al. (2015) [124]	HFD-fed C57BL/6J mice; db/db mice	1, 3, 10, or 30 mg/kg body weight of Piceatannol solution (8 mL/kg in 0.5% CMC) once a day for 5 weeks	↔ Body weight and visceral adiposity; ↓ fasting blood glucose; ↓ postprandial hyperglycemia	Demonstrated glucose-regulatory activity despite limited anti-obesity effects.
Ishihata et al. (2016) [125]	HFD-fed Fischer 344 rats	HF diets containing PFSE (0.5% *w*/*w*) for 16 weeks	↔ Body weight and adiposity; ↓ hyperglycemia; modest improvement in serum lipids	Selected metabolic improvements were observed following PFSE administration without significant reductions in body weight or adiposity
Hijona et al. (2016) [126]	Obese Zucker rats	15 or 45 mg/kg body weight/day Piceatannol, oral gavage, 6 weeks	↔ Body weight and adiposity; modest improvement in glycemic control; ↓ LDL-C; ↓ non-esterified fatty acids; gut microbiota modulation	Therapeutic efficacy appears attenuated in severe genetic obesity; however, one study cannot establish that genetic obesity or its severity explains the absence of weight loss.
Lee et al. (2019) [127]	HFD-fed C57BL/6J mice	10 mg/kg/day Picaetannol, oral gavage, 4 weeks	↔ Body weight; ↑ glucose tolerance; ↓ hepatic steatosis; ↑ hepatic SIRT1/SIRT3 expression	Improvements in selected glucose-related and hepatic lipid endpoints were accompanied by changes in hepatic molecular markers.
Minakawa et al. (2012) [128]	db/db mice (type 2 diabetes)	5 mg/100 g/day Piceatannol, oral gavage, 3 weeks	↓ Fasting blood glucose; ↑ skeletal muscle glucose uptake	First in vivo evidence supporting the potential antihyperglycemic activity of piceatannol.

* **Abbreviations:** CMC, carboxymethylcellulose; FFAs, free fatty acids; HF, high-fat; HFD, high-fat diet; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; PFSE, passion fruit seed extract; SIRT1, sirtuin 1; SIRT3, sirtuin 3; *w*/*w*, weight per weight. # **Notes:** ↑, increase; ↓, decrease; ↔, no significant change. The db/db mouse is a genetically diabetic model characterized by defective leptin receptor signaling. Where the term "piceatannol" is used without further specification, it refers to purified piceatannol. Findings obtained with piceatannol-rich passion fruit seed extract (PFSE) should not be attributed exclusively to piceatannol.

6.1. Evidence from Experimental Animal Models of Obesity and Metabolic Dysfunction: Effects on Body Weight, Adiposity, and Adipocyte Morphology

Animal investigations report reductions in body weight gain or adiposity in some, but not all, obesity models. Interpretation requires separating changes in body mass, adipose depot weights, and adipocyte morphology from direct measures of adipose tissue function, which have been assessed less extensively.

6.1.1. Effects on Body Weight and Adiposity in Experimental Models

Tung et al. (2016) administered purified piceatannol (0.1% or 0.25% *w*/*w* in the diet) for 18 weeks to male C57BL/6 mice fed a high-fat diet [77]. Body weight gain decreased without a reported change in food intake, perigonadal and retroperitoneal adipose depot weights and perigonadal adipocyte size were also reduced [77]. These findings document improvements in adiposity and adipocyte morphology, but do not establish restoration of adipose tissue function because fibrosis, vascular remodeling, hypoxia, and immune-cell composition were not comprehensively assessed.

In ovariectomized female C57BL/6J mice, Arisawa et al. (2023) found that 0.25% dietary piceatannol for 12 weeks attenuated weight gain and visceral adipose accumulation without changing food intake [122]. White adipose tissue weight was reduced, with increased hormone-sensitive lipase phosphorylation in white adipose tissue and changes in the SIRT1/PGC-1α/UCP1 pathway in brown adipose tissue [122]. Because the reported benefits were largely restricted to ovariectomized animals, a possible influence of estrogen-deficient status warrants investigation rather than a general conclusion about efficacy across obesity phenotypes.

Sun et al. (2025) reported reduced body weight gain, relative weights of epididymal, inguinal, and perirenal white adipose depots, and adipocyte hypertrophy after intraperitoneal administration of purified piceatannol (12.84 mg/kg/day for 14 weeks) to high-fat diet-fed male C57BL/6J mice [123]. Energy intake was not altered. Piceatannol produced larger effects on these endpoints than resveratrol within this particular experimental comparison; this does not establish superior efficacy across models or in humans [123].

Although these three investigations reported favorable changes in selected weight- or adiposity-related endpoints, they differed in animal sex and hormonal status, intervention route, dose, and duration. Moreover, unchanged food or energy intake in individual studies does not establish increased energy expenditure or identify the physiological mechanisms underlying reduced weight gain. Direct measurements of energy expenditure, body composition, and tissue-specific piceatannol exposure were not consistently available across these investigations [77,122,123].

6.1.2. Studies Reporting Limited Effects on Obesity-Related Phenotypes

In contrast, Uchida-Maruki et al. (2015) observed no significant reduction in weight gain, visceral adipose mass, or food intake after five weeks of purified piceatannol treatment in high-fat diet-fed C57BL/6J mice [124]. Although the study also included db/db mice treated with purified piceatannol or piceatannol-rich passion fruit seed extract (PFSE), obesity-related endpoints were not assessed in that model [124].

Ishihata et al. (2016) likewise reported no significant reduction in weight gain or adiposity with piceatannol-rich PFSE in high-fat diet-fed Fischer 344 rats [125]. Because PFSE contains other constituents, findings from this preparation cannot be attributed exclusively to piceatannol.

In genetically obese Zucker rats, Hijona et al. (2016) found no significant changes in body weight gain, adiposity, or food intake after six weeks of oral purified piceatannol (15 or 45 mg/kg/day) [126]. This null result underscores the need to distinguish metabolic effects from changes in body mass, without establishing that genetic obesity itself explains the difference between studies.

Lee et al. (2019) similarly observed no significant changes in final body weight or adipose tissue mass in high-fat diet-fed C57BL/6J mice, despite changes in glucose-related and hepatic outcomes [127]. Thus, improvements in selected metabolic endpoints need not coincide with reduced adiposity.

Collectively, these null findings demonstrate that favorable changes in selected glucose-regulatory, hepatic, or circulating metabolic outcomes do not necessarily coincide with reductions in body weight or adiposity [124–127]. However, the differences between studies do not establish that particular obesity models are inherently resistant to piceatannol, because intervention dose, duration, route, formulation, animal characteristics, and outcome assessment methods were not standardized. In addition, the findings obtained with piceatannol-rich passion fruit seed extract [125] should be interpreted separately from those obtained with purified piceatannol.

6.1.3. Critical Appraisal

The available animal evidence for reductions in body weight and adiposity following piceatannol administration remains limited, heterogeneous, and model-dependent. Among the seven investigations explicitly reporting body-weight or adiposity outcomes summarized in this section, three reported significant reductions in selected measures of weight gain, adipose depot mass, or adipocyte hypertrophy [77,122,123], whereas four did not demonstrate significant reductions in body weight or adiposity [124–127]. Importantly, these findings were obtained across different experimental settings, including high-fat diet-induced obesity in C57BL/6 or C57BL/6J mice, ovariectomy-associated obesity in female C57BL/6J mice, high-fat diet-fed Fischer 344 rats, and genetically obese Zucker rats. The studies also differed in sex, administered dose, treatment duration (4–18 weeks), route of administration (dietary supplementation, oral administration, or intraperitoneal injection), and formulation (purified piceatannol versus piceatannol-rich passion fruit seed extract). Furthermore, the available investigations did not uniformly assess food intake, energy expenditure, body composition, or tissue exposure to piceatannol and its metabolites. Consequently, the observed differences cannot be confidently attributed to particular animal models, doses, administration routes, or treatment durations. The available evidence therefore supports selected model-specific effects on body weight and adiposity rather than moderate, strong, or consistently reproducible anti-obesity efficacy.

A central evidence gap is the limited characterization of adipose-tissue function beyond depot mass and adipocyte size. Although reductions in adiposity and adipocyte hypertrophy have been reported in selected animal models [77,122,123], these outcomes do not establish restoration of the structural, vascular, endocrine, immunological, or metabolic functions of adipose tissue. In particular, direct evidence remains insufficient regarding the effects of piceatannol on adipose fibrosis and extracellular-matrix remodeling, vascular density and angiogenesis, tissue oxygenation and hypoxia, immune-cell composition and recruitment, adipokine secretion, adipocyte turnover, and adipose-tissue expandability. Furthermore, changes in whole-body glucose homeostasis or selected insulin-signaling proteins cannot be interpreted as definitive evidence of improved insulin responsiveness within specific adipose depots. Consequently, the available animal studies support changes in selected adiposity-related and metabolic outcomes, rather than comprehensive functional restoration of adipose tissue.

6.2. Evidence from Experimental Animal Models of Obesity and Metabolic Dysfunction: Effects on Glucose Homeostasis and Insulin Sensitivity

Animal studies suggest that piceatannol may improve glucose homeostasis in selected models of obesity and diabetes, but the endpoints examined differ substantially. Fasting glycemia, glucose tolerance, insulin sensitivity, and associated molecular markers should therefore be interpreted separately [77,123–128].

6.2.1. Glucose-Regulatory Outcomes in Experimental Models

Sun et al. (2025) reported reductions in fasting glucose and HOMA-IR, together with improvements in glucose-tolerance outcomes, in high-fat diet-fed mice treated with piceatannol [123]. These findings suggest favorable changes in glucose homeostasis and fasting-state indices associated with insulin resistance. However, HOMA-IR is a surrogate measure, and improved glucose tolerance does not independently establish enhanced insulin sensitivity, since the observed response may involve changes in insulin secretion, hepatic glucose production, peripheral glucose disposal, or other components of glucose regulation. The interpretation of insulin sensitivity should therefore depend on whether the original investigation included additional dynamic or direct measurements of insulin responsiveness. Hepatic metabolomic and molecular changes accompanied these responses. Although the study also found greater improvement than resveratrol under its specific experimental conditions, the findings do not establish general superiority or demonstrate which molecular changes caused the glycemic effects [123].

Lee et al. (2019) observed improved glucose tolerance in high-fat diet-fed mice, together with increased hepatic expression of the insulin receptor, SIRT1, and SIRT3 [127]. These molecular observations are consistent with altered metabolic regulation, but direct causal involvement in the glucose response was not established. Importantly, increased expression of SIRT1, SIRT3, or insulin-signaling proteins should not be interpreted as direct evidence of improved hepatic or mitochondrial function. Such conclusions would require complementary functional measurements, including appropriate assessments of hepatic metabolic activity, mitochondrial respiration, oxidative phosphorylation, or mitochondrial enzyme activity. Therefore, the findings support changes in selected hepatic molecular markers alongside improved glucose tolerance, rather than demonstrating functional restoration of hepatic or mitochondrial metabolism.

6.2.2. Evidence Supporting Improved Glycemic Control

Minakawa et al. (2012) reported lower fasting blood glucose concentrations after administration of purified piceatannol in db/db mice [128]. The study supports an antihyperglycemic effect in that model but does not by itself establish improved insulin sensitivity.

Uchida-Maruki et al. (2015) reported lower fasting glucose in high-fat diet-fed mice and attenuation of postprandial hyperglycemia after glucose loading in db/db mice treated with either purified piceatannol or piceatannol-rich PFSE [124]. The latter extract results should be interpreted as effects of the preparation rather than of isolated piceatannol, and the mechanisms underlying the glycemic response were not directly characterized [124].

Tung et al. (2016) found reduced fasting blood glucose in high-fat diet-fed mice [77]. Because glucose tolerance, circulating insulin, and direct indices of insulin responsiveness were not examined, this finding supports a glucose-lowering effect but not a specific conclusion about insulin sensitivity.

Ishihata et al. (2016) reported amelioration of hyperglycemia with piceatannol-rich PFSE in 344 high-fat diet-fed Fischer rats [125]. Insulin sensitivity and glucose-regulatory pathways were not directly assessed, and the contribution of piceatannol relative to other extract constituents remains uncertain.

6.2.3. Studies Demonstrating Limited Metabolic Efficacy

Hijona et al. (2016) observed only modest glycemic improvement in genetically obese Zucker rats, without convincing evidence of improved insulin sensitivity [126]. This contrasts with several diet-induced models, although between-study differences preclude attributing the discrepancy specifically to genetic obesity.

6.2.4. Critical Appraisal

Overall, several studies report reductions in fasting glucose, while fewer directly assess glucose tolerance or insulin sensitivity [77,123–128]. The integrated glycemic and molecular measurements of Sun et al. (2025) and the hepatic expression data of Lee et al. (2019) add mechanistic context, but do not establish causality between specific signaling changes and whole-body glucose regulation [123,127].

An important limitation is the heterogeneity of glucose-regulatory endpoints across the available animal studies. Reductions in fasting glucose, improvements in glucose tolerance, changes in HOMA-IR, and alterations in insulin-signaling proteins represent distinct levels of evidence and should not be interpreted interchangeably as demonstrating improved insulin sensitivity. In particular, direct assessment of tissue-specific insulin action and appropriate functional validation of molecular signaling changes remain limited. Consequently, conclusions regarding the glucose-regulatory effects of piceatannol should be restricted to the specific endpoints measured in each investigation [77,123–128].

The main unresolved questions concern tissue-specific insulin action, durability of glycemic responses, and comparability of purified piceatannol with complex extracts. These limitations should guide interpretation of glucose-related efficacy and are considered further in Section 6.5.

6.3. Evidence from Experimental Animal Models of Obesity and Metabolic Dysfunction: Limited Evidence for Anti-Inflammatory Effects

Direct in vivo evidence of anti-inflammatory activity following piceatannol administration is considerably more limited than the evidence concerning selected metabolic outcomes. Importantly, inflammatory endpoints should be interpreted according to their biological compartment and assessment method, distinguishing hepatic cytokine mRNA or protein expression, circulating cytokine concentrations, adipose-tissue cytokine expression, immune-cell infiltration, macrophage abundance and phenotype, inflammasome activation, and histological evidence of inflammation. These outcomes are not interchangeable, and changes in one tissue or inflammatory marker cannot establish generalized anti-inflammatory activity. In particular, reduced hepatic cytokine expression does not demonstrate attenuation of adipose-tissue inflammation, systemic inflammation, or adipocyte–macrophage inflammatory interactions. Studies reporting metabolic or molecular changes without direct inflammatory measurements should therefore not be classified as demonstrating anti-inflammatory effects.

6.3.1. Inflammatory Outcomes in Experimental Models

Sun et al. (2025) reported reduced hepatic expression of TNF-α and IL-6 in high-fat diet-fed mice receiving piceatannol [123]. These findings indicate changes in selected liver-associated inflammatory markers but do not establish reduced circulating cytokine concentrations, diminished inflammatory signaling in adipose tissue, altered macrophage recruitment or polarization, or systemic anti-inflammatory efficacy. Furthermore, the interpretation should distinguish cytokine mRNA expression from protein abundance, since transcriptional changes do not necessarily correspond to changes in cytokine production or secretion. Greater reductions than those observed with resveratrol were reported within this specific experimental comparison [123]; however, these findings should not be generalized to other inflammatory tissues or models.

Lee et al. (2019) observed increased hepatic SIRT1 and SIRT3 expression [127]. Because cytokines, inflammatory cell infiltration, and inflammatory signaling were not directly assessed, these results should not be classified as direct evidence of anti-inflammatory efficacy.

Accordingly, the hepatic cytokine findings of Sun et al. (2025) provide direct but tissue-limited evidence, whereas the findings of Lee et al. (2019) are mechanistically suggestive rather than confirmatory [123,127].

6.3.2. Studies Without Direct Assessment of Inflammatory Outcomes

Several animal investigations reported favorable metabolic, adiposity-related, hepatic, or vascular outcomes without directly assessing inflammatory responses. Specifically, Tung et al. [77], Arisawa et al. [122], Ishihata et al. [125], and Hijona et al. [126] did not comprehensively evaluate inflammatory cytokines, macrophage infiltration or polarization, or tissue-specific inflammatory signaling. Although these investigations contribute to the understanding of piceatannol-associated metabolic effects, their findings cannot establish anti-inflammatory efficacy. Importantly, the absence of inflammatory measurements should not be interpreted as evidence that no anti-inflammatory effects occurred. Rather, the contribution of inflammatory mechanisms to the observed metabolic responses remains unresolved.

6.3.3. Critical Appraisal

The available animal evidence for anti-inflammatory activity of piceatannol in obesity-associated metabolic dysfunction remains very limited and is largely restricted to selected hepatic inflammatory markers. Among the animal investigations discussed in this section, Sun et al. [123] reported changes in hepatic TNF-α and IL-6 expression, whereas several other studies primarily assessed metabolic, hepatic, vascular, or oxidative outcomes without directly evaluating inflammatory responses [77,122,125–127]. Consequently, the current evidence does not establish consistent anti-inflammatory activity across adipose tissue, the systemic circulation, or other metabolically relevant compartments.

Importantly, hepatic cytokine mRNA or protein measurements, circulating cytokine concentrations, adipose-tissue inflammatory mediator expression, macrophage infiltration, macrophage phenotype, inflammasome activation, and histological inflammation represent distinct levels of evidence. Changes in hepatic TNF-α or IL-6 expression cannot independently establish reduced systemic inflammation, attenuation of adipose-tissue macrophage recruitment, polarization toward an anti-inflammatory macrophage phenotype, or remodeling of the adipose-tissue immune microenvironment. Likewise, changes in hepatic SIRT1/SIRT3 expression or improvements in body weight, glucose regulation, and lipid metabolism should not be interpreted as direct evidence of anti-inflammatory efficacy.

Furthermore, the adipocyte–macrophage interactions and inflammatory signaling pathways investigated in cellular systems, including NF-κB, JNK, p38 MAPK, and potentially NLRP3-associated responses, have not been adequately validated as causal mechanisms in the available obesity-related animal studies. In particular, the current evidence does not establish that piceatannol modifies adipose-tissue immune-cell composition, macrophage phenotype, or inflammasome activation in vivo, nor does it demonstrate that such changes mediate improvements in metabolic outcomes. Therefore, the available animal findings should be interpreted as preliminary, tissue-limited observations rather than evidence of generalized anti-inflammatory efficacy or validation of cellular adipocyte–macrophage mechanisms.

Future animal investigations should incorporate compartment-specific inflammatory phenotyping, including circulating cytokine measurements, adipose-tissue cytokine mRNA and protein expression, immunohistochemical or flow-cytometric assessment of immune-cell infiltration, macrophage phenotyping, inflammasome activation markers, and histological characterization of tissue inflammation. These measurements should ideally be integrated with pharmacokinetic characterization, direct pathway assessments, and appro-

priately designed mechanistic interventions to determine whether inflammatory changes contribute causally to metabolic outcomes.

6.4. Evidence from Experimental Animal Models of Obesity and Metabolic Dysfunction: Effects on Lipid Metabolism

Animal studies have examined both hepatic lipid accumulation and circulating lipid concentrations after piceatannol administration. These distinct outcomes may provide evidence of potential lipid-modulating effects, but findings differ by model and lipid endpoint [77,122–127].

6.4.1. Lipid-Regulatory Outcomes in Experimental Models

Tung et al. (2016) reported reductions in circulating total cholesterol, LDL-cholesterol, triglycerides, and hepatic lipid accumulation following piceatannol administration in high-fat diet-fed mice [77]. Lee et al. (2019) observed attenuation of hepatic steatosis accompanied by increased hepatic SIRT1 and SIRT3 expression, although the causal involvement of these molecular changes was not established [127]. Sun et al. (2025) identified alterations in hepatic lipid-related metabolomic pathways, providing evidence of changes in metabolic profiles rather than direct confirmation of improved hepatic lipid handling [123]. Collectively, these findings indicate potentially favorable effects on selected lipid-related endpoints, while emphasizing the need to distinguish circulating lipid concentrations, hepatic steatosis, and metabolomic changes as separate outcomes.

6.4.2. Evidence Supporting Improvements in Systemic Lipid Homeostasis

Arisawa et al. (2023) observed lower serum total cholesterol in ovariectomized mice receiving piceatannol [122]. Because hepatic lipid accumulation was not directly investigated, the study contributes evidence for a circulating lipid outcome rather than for reversal of hepatic steatosis.

In genetically obese Zucker rats, Hijona et al. (2016) found reductions in LDL-cholesterol and non-esterified fatty acids, but no significant changes in total cholesterol, HDL-cholesterol, triglycerides, or hepatic steatosis [126]. This selective response illustrates why lipid endpoints should not be summarized as uniformly improved.

6.4.3. Studies Providing Limited Evidence for Lipid Regulation

Uchida-Maruki et al. (2015) primarily assessed glucose-related outcomes and provided limited lipid-specific evidence [124]. It therefore contributes little to conclusions about hepatic lipid regulation.

Ishihata et al. (2016) investigated piceatannol-rich PFSE and reported selected metabolic and vascular outcomes, but did not comprehensively assess hepatic lipid pathways [125]. The study should not be taken as direct mechanistic validation of purified piceatannol's lipid-regulatory actions.

6.4.4. Critical Appraisal

The clearest lipid-related findings are reductions in hepatic lipid accumulation or steatosis in selected studies [77,127] and improvements in particular circulating lipid measures in others [77,122,126]. Sun et al. (2025) adds metabolomic evidence of hepatic pathway changes, which is informative but not equivalent to direct functional validation [123].

These results are heterogeneous across outcomes and models, and the contribution of fatty acid oxidation, lipid transport, and tissue-specific regulatory pathways remains incompletely defined. Therefore, conclusions about whole-body lipid homeostasis should remain more cautious than conclusions about individual measured endpoints.

Future studies should pair quantitative hepatic lipid measurements with circulating lipid panels and targeted functional assays to clarify whether observed molecular changes account for the physiological responses.

6.5. Integrated Interpretation of the In Vivo Evidence and Translational Perspectives

Across the available animal investigations, the evidence for body-weight reduction and decreased adiposity remains limited, heterogeneous, and model-dependent. Of the seven studies explicitly evaluating these outcomes discussed in Section 6.1, three reported favorable changes in selected weight- or adiposity-related endpoints [77,122,123], whereas four reported no statistically significant reductions [124–127]. These findings were obtained using different species, strains, obesity models, treatment doses, administration routes, durations, and formulations, including purified piceatannol and piceatannol-rich botanical extracts. Furthermore, food intake, energy expenditure, body composition, and tissue exposure were not uniformly characterized. Although selected investigations also reported changes in glucose regulation, hepatic lipid metabolism, and circulating metabolic biomarkers, these effects were not consistently accompanied by reductions in body weight or adiposity. Consequently, the available findings do not establish reproducible anti-obesity efficacy across experimental models, and differences between studies cannot currently be attributed to specific experimental characteristics with confidence.

An additional limitation concerns the comparability of administered doses across investigations. Dietary concentrations expressed as percentage weight/weight are not directly equivalent to body-weight-adjusted doses administered by injection or gavage. Furthermore, estimated dietary intake depends on food consumption and body weight, while the corresponding systemic exposure may vary according to absorption, metabolism, formulation, and administration route. These differences should be considered when comparing experimental findings across studies.

The interpretation of lipolysis-related findings also requires particular caution. Kwon et al. (2022) reported suppression of adipocyte lipolysis associated with autophagy–lysosome-dependent degradation of ATGL, CGI-58, and PLIN1, whereas Arisawa et al. (2023) reported increased lipolysis-associated responses in ovariectomized female mice [121,122]. These findings were obtained under different experimental conditions and should not be combined into a generalized conclusion that piceatannol stimulates lipid mobilization. Moreover, reduced lipid accumulation during adipocyte differentiation is not equivalent to increased triglyceride hydrolysis in mature adipocytes. Direct measurements of lipolytic flux, circulating and tissue-specific fatty-acid turnover, and relevant regulatory mechanisms are required to determine whether the apparently divergent findings reflect biological context, experimental design, or differences in outcome assessment.

Associations between molecular adaptations and physiological outcomes do not establish causal target engagement. Although selected animal investigations have reported favorable changes in body weight, adiposity, glucose regulation, hepatic lipid accumulation, and circulating metabolic biomarkers, these outcomes cannot independently demonstrate that the molecular pathways identified in cultured adipocytes mediated the observed in vivo responses [77,122–128]. Similarly, changes in hepatic gene expression, SIRT1/SIRT3 abundance, or metabolomic profiles provide complementary molecular information but do not establish direct target engagement, pathway necessity, or causal mediation [123,127]. Furthermore, alterations in hepatic gene or protein expression, including changes in SIRT1, SIRT3, and other metabolic regulators, should not be regarded as direct evidence of improved hepatic or mitochondrial function. Functional conclusions require appropriate physiological or biochemical measurements, such as hepatic metabolic flux, mitochondrial oxygen consumption, respiratory-chain activity, ATP production, or substrate oxidation,

depending on the proposed mechanism. Accordingly, the available molecular findings should be interpreted as evidence of altered metabolic signaling rather than definitive demonstration of restored organ or mitochondrial function. Such conclusions would require additional evidence, including quantitative assessment of tissue exposure to parent piceatannol and relevant metabolites, direct measurements of target engagement or pathway activity, selective pharmacological inhibition or genetic loss-of-function approaches, and tissue-specific metabolic flux analyses. Many cellular hypotheses, particularly those involving adipose immune remodeling, fibrosis, hypoxia, and adipokine signaling, have not been systematically tested in intact animals. Accordingly, the available animal studies should be interpreted as providing model-specific physiological and molecular observations that may be compatible with selected cellular mechanisms, rather than definitive validation of those mechanisms in vivo.

The evidence for anti-inflammatory activity in obesity-related animal models is particularly limited. The available findings are largely restricted to selected hepatic cytokine measurements, while direct assessments of circulating inflammatory mediators, adipose-tissue cytokines, immune-cell infiltration, macrophage phenotype, inflammasome activation, and histological inflammation remain insufficiently characterized [123]. Consequently, hepatic inflammatory marker changes cannot be extrapolated to generalized systemic or adipose-tissue anti-inflammatory effects. Moreover, the adipocyte–macrophage signaling mechanisms identified in cellular experiments have not been demonstrated to mediate metabolic responses in vivo.

A further limitation concerns the distinction between changes in adipose-tissue morphology and restoration of adipose-tissue function. Although reductions in adipocyte size or adipose depot mass may indicate alterations in lipid accumulation, they do not independently demonstrate improvements in extracellular-matrix organization, fibrosis, vascularization, tissue oxygenation, immune-cell composition, endocrine activity, or adipocyte turnover. Similarly, systemic improvements in glucose tolerance or insulin-related biomarkers cannot establish enhanced insulin responsiveness within individual adipose depots without tissue-specific functional measurements. Accordingly, claims regarding improved adipose-tissue function should remain provisional until these structural, immunological, endocrine, and metabolic dimensions have been directly evaluated in appropriately designed in vivo investigations.

Experimental context may influence response, but the small evidence base does not support firm model-specific predictions. Diet-induced and ovariectomy-associated models have yielded favorable results for some endpoints, whereas genetically obese models have shown more selective responses [77,122–127]. Differences in intervention protocols and outcome definitions complicate attribution of these contrasts to disease phenotype or hormonal status.

Interpretation also depends on preparation and exposure. Purified piceatannol and piceatannol-rich PFSE are not interchangeable interventions; effects of the latter cannot be assigned exclusively to piceatannol [124,125]. Botanical extracts contain multiple phytochemical constituents that may contribute independently or through interactions to the observed biological responses. Furthermore, differences in the concentration of piceatannol, extract composition, and the administered quantity of the active compound complicate direct comparisons with studies using purified piceatannol. Consequently, findings from extract-based investigations should be interpreted as evidence for the biological activity of the investigated preparation rather than definitive evidence of the pharmacological efficacy of isolated piceatannol. In particular, comparisons between purified piceatannol and PFSE require reporting of the extract's standardized piceatannol content, total administered extract dose, corresponding piceatannol-equivalent dose, and relevant coex-

isting phytochemicals, ideally alongside a purified-piceatannol comparator administered at an equivalent dose. Such information is not uniformly available across the included studies [124,125]. Differences in dose, route of administration, bioavailability, metabolism, and study duration further restrict extrapolation to human use.

The principal preclinical priorities are independent replication using standardized endpoints, pharmacokinetic characterization at relevant doses, and direct testing of proposed mechanisms in target tissues. Comparative studies of purified piceatannol and chemically characterized extracts would also help distinguish compound-specific from mixture-related effects.

From an evidence-certainty perspective, the available animal studies should be interpreted primarily as providing model-specific functional evidence. Improvements in body weight, adiposity, glucose tolerance, or lipid-related outcomes may demonstrate biological responses under the investigated experimental conditions, but do not necessarily establish the causal involvement of the proposed molecular pathways. Furthermore, the relatively small number of independent investigations, differences in animal models and treatment protocols, and incomplete replication of individual endpoints limit conclusions regarding reproducible preclinical efficacy. Accordingly, the evidence supports continued mechanistic and translational investigation but remains insufficient to establish generalized anti-obesity efficacy across experimental models.

Furthermore, reported improvements in glucose homeostasis should not be interpreted uniformly as enhanced insulin sensitivity. The available investigations employed heterogeneous endpoints, including fasting glycemia, glucose-tolerance measurements, HOMA-IR, and selected molecular markers, which assess different components of glucose regulation. Without appropriate direct physiological measurements, the relative contributions of insulin secretion, hepatic glucose production, and peripheral insulin-mediated glucose disposal remain uncertain.

Because no formal study-level risk-of-bias assessment or evidence-certainty grading was performed, the present narrative synthesis does not assign comparative certainty rankings to individual animal investigations or establish the superiority of particular experimental findings. Instead, conclusions are based on the specific outcomes measured, consistency across studies, methodological limitations, and the extent of independent replication.

Thus, current animal findings support biological plausibility rather than established anti-obesity or metabolic therapeutic efficacy. The strength of evidence differs across endpoints, and clinical relevance remains uncertain until reproducible physiological effects and exposure–response relationships are established. Figure 3 summarizes the principal molecular mechanisms proposed from the combined cellular and animal evidence; these pathways differ in the extent of direct in vivo validation.

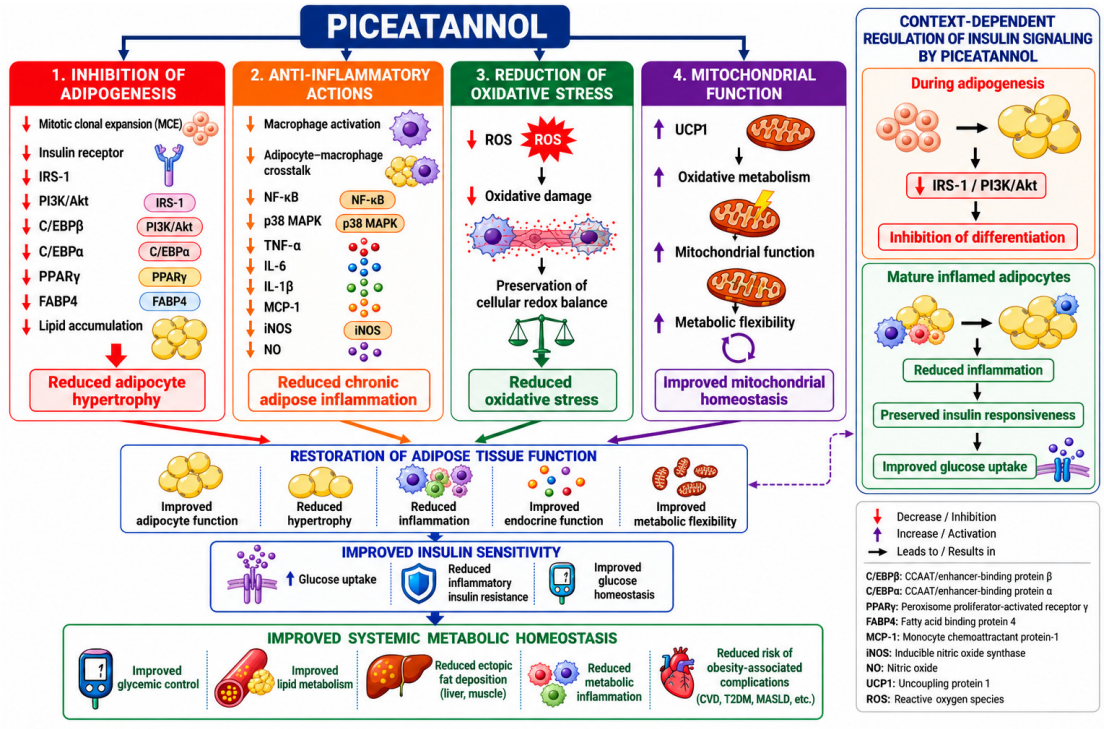


Figure 3. Proposed molecular mechanisms and experimentally observed metabolic effects of piceatannol: integration of cellular and animal evidence.

7. Human Evidence and Translational Perspectives

Following the mechanistic evidence derived from cellular studies (Section 5) and the assessment of selected physiological and metabolic outcomes in experimental animal models (Section 6), human investigations provide an opportunity to examine whether piceatannol produces measurable biological or clinical effects in humans. However, molecular associations observed in cellular studies and functional responses reported in animals do not establish that the same mechanisms operate in humans or result in clinically meaningful benefits. Human investigations must therefore be interpreted according to the outcomes assessed, distinguishing pharmacokinetic measurements, molecular and cardiometabolic biomarkers, clinical efficacy, and safety. Short-term changes in surrogate endpoints may provide preliminary evidence of biological activity but are insufficient to establish therapeutic effectiveness or long-term safety.

Although the available clinical evidence remains relatively limited and heterogeneous, it provides the first opportunity to assess the potential therapeutic relevance of piceatannol in humans. Accordingly, this section critically evaluates the current clinical literature, emphasizing the extent to which the biological activities identified in experimental studies are supported in human populations, while highlighting the principal limitations of the available evidence and the remaining challenges for clinical translation.

An important consideration when interpreting human evidence is the distinction between clinical investigations administering purified piceatannol and those evaluating piceatannol-rich botanical preparations. Trials involving purified piceatannol provide more direct evidence concerning the effects of the isolated compound, whereas studies using botanical extracts assess the effects of multicomponent interventions whose biological activity may reflect contributions from piceatannol and other phytochemical constituents. Differences in extract standardization, piceatannol content, administered dose, and potential matrix-dependent effects on bioavailability further limit direct comparisons between these intervention categories. Accordingly, the clinical findings discussed below are interpreted

in relation to the specific preparation administered, and outcomes observed with botanical extracts are not attributed exclusively to piceatannol [82–84,129–131]. Importantly, clinical investigations primarily designed to evaluate dermatological outcomes are considered only as complementary evidence regarding the short-term tolerability of the specific preparations administered. Improvements in skin hydration, wrinkle-related parameters, or other dermatological endpoints are not interpreted as evidence of metabolic efficacy or clinically meaningful benefits for obesity-associated metabolic dysfunction.

7.1. Cardiometabolic Outcomes

An important randomized clinical investigation of piceatannol was conducted by Kitada et al. (2017) in a randomized, double-blind, placebo-controlled trial involving 39 normal-weight and overweight adults who received either piceatannol (20 mg/day) or placebo for 8 weeks [82]. The findings were mixed, with statistically favorable changes in selected cardiometabolic parameters but no significant improvements in several other metabolic and physiological outcomes. Specifically, piceatannol supplementation was associated with reductions in fasting insulin concentrations, the homeostatic model assessment of insulin resistance (HOMA-IR), systolic and diastolic blood pressure, and heart rate in the subgroup of overweight men [82]. In contrast, no significant improvements were observed in fasting glucose, body weight, body composition, circulating lipid concentrations, endothelial function, inflammatory or oxidative stress biomarkers, or peripheral blood SIRT1 and AMPK-related markers [82]. Furthermore, the favorable cardiometabolic findings were not consistently observed in women or normal-weight participants. Thus, the trial demonstrated a heterogeneous pattern of positive and null outcomes rather than consistent cardiometabolic benefits across the overall study population.

Taken together, the positive and null findings of Kitada et al. (2017) indicate that the clinical effects of piceatannol remain uncertain and may differ across cardiometabolic endpoints and participant subgroups [82]. Although the reductions in fasting insulin, HOMA-IR, blood pressure, and heart rate observed in overweight men provide preliminary evidence of possible biological activity, these favorable findings should be interpreted alongside the absence of significant improvements in body weight, body composition, fasting glucose, circulating lipids, endothelial function, and several inflammatory, oxidative, and molecular biomarkers. Moreover, stratification according to sex and body weight resulted in relatively small subgroup sizes, reducing statistical power. The evaluation of multiple cardiometabolic outcomes across participant subgroups also raises concerns regarding multiplicity and the possibility of chance-positive findings, particularly in the absence of clearly established adjustment for multiple comparisons. Consequently, neither the favorable subgroup-specific findings nor the nonsignificant outcomes provide a definitive assessment of clinical efficacy. The available evidence does not establish an anti-obesity effect of piceatannol in humans, and the observed cardiometabolic responses require independent confirmation in adequately powered randomized controlled trials with prespecified outcomes and appropriate statistical control for multiplicity.

Importantly, HOMA-IR is a surrogate index derived from fasting glucose and insulin concentrations and should not be considered equivalent to directly measured insulin sensitivity. Therefore, the observed reduction in HOMA-IR suggests a favorable change in a fasting-state index associated with insulin resistance but does not establish improved peripheral insulin-stimulated glucose disposal or tissue-specific insulin responsiveness. The absence of direct measurements, such as hyperinsulinemic–euglycemic clamp assessments, limits the physiological interpretation of these findings [82].

7.2. Molecular and Energy-Metabolism Outcomes

Whether molecular pathways implicated in the experimental effects of piceatannol are similarly affected in humans has been investigated in a limited number of clinical studies. Among these, Tanaka et al. (2024) evaluated changes in molecular biomarkers following piceatannol supplementation [129]. Administration of 100 mg/day of piceatannol for 2 weeks increased whole-blood SIRT1 mRNA expression compared with placebo, while complementary in vitro experiments demonstrated increased expression of genes associated with mitochondrial biogenesis and fatty acid utilization [129]. These findings provide preliminary evidence of an increase in whole-blood SIRT1 transcript abundance following piceatannol supplementation, rather than direct evidence of SIRT1 activation in metabolically relevant tissues. Importantly, SIRT1 protein abundance and enzymatic activity were not demonstrated to increase in skeletal muscle, adipose tissue, or liver, and the observed whole-blood mRNA response does not establish molecular target engagement in these organs. Furthermore, the accompanying in vitro findings cannot be extrapolated to demonstrate improved mitochondrial biogenesis, mitochondrial function, insulin sensitivity, or whole-body energy metabolism in humans. Accordingly, the clinical findings should be interpreted as preliminary evidence of a circulating transcriptional biomarker response rather than confirmation of the metabolic mechanisms or physiological benefits proposed from experimental studies [129].

By contrast, Kasai et al. (2025) found that supplementation with 10 mg/day of piceatannol for 7 days did not modify resting, exercise-induced, or post-exercise fat oxidation in eight healthy, physically active men [130]. Likewise, no significant changes were observed in respiratory exchange ratio, oxygen consumption, circulating free fatty acids, glycerol, ketone bodies, insulin, or other metabolic hormones [130]. Although the study was limited by its small sample size, short intervention period, and inclusion of metabolically healthy participants, these findings suggest that short-term piceatannol supplementation does not acutely enhance whole-body energy metabolism under physiological conditions [130].

Collectively, these studies highlight an important challenge in the clinical translation of piceatannol. Although changes in selected molecular biomarkers have been observed in humans, direct molecular target engagement and corresponding improvements in clinically relevant metabolic outcomes have not been established. This apparent discrepancy underscores the complexity of translating mechanistic and preclinical findings into clinically meaningful outcomes and emphasizes the need for larger, longer-duration randomized controlled trials incorporating both mechanistic biomarkers and comprehensive metabolic phenotyping to determine whether sustained modulation of these molecular pathways ultimately results in clinically relevant metabolic benefits.

7.3. Safety and Tolerability

The limited available human studies have not identified major tolerability concerns during short-term administration of the investigated piceatannol preparations and doses. However, the small sample sizes, short follow-up periods, and limited systematic assessment of adverse events prevent firm conclusions regarding uncommon adverse effects, dose-dependent toxicity, or long-term safety.

The principal metabolic trial by Kitada et al. (2017) demonstrated that supplementation with 20 mg/day of purified piceatannol for eight weeks was not associated with clinically significant adverse events or abnormalities in routine biochemical or hematological parameters, supporting the short-term tolerability of this dose in healthy and overweight adults [82].

Additional preparation-specific tolerability information is available from randomized controlled trials investigating piceatannol-containing preparations for dermatological indi-

cations. Maruki-Uchida et al. (2018) reported that supplementation with a passion fruit seed extract providing approximately 5 mg/day of piceatannol for eight weeks improved selected skin hydration outcomes without serious adverse events [83]. Similarly, Seto et al. (2026) investigated a beverage providing 10 mg/day of piceatannol for eight weeks and reported improvements in selected skin hydration and wrinkle-related outcomes without clinically important adverse events [84]. However, the findings of these studies should be interpreted in relation to the specific administered formulations. In particular, the effects of multicomponent preparations cannot be attributed exclusively to piceatannol, and their tolerability profiles cannot automatically be extrapolated to purified piceatannol. Moreover, these trials were designed primarily to investigate dermatological outcomes rather than metabolic efficacy or comprehensive safety. Therefore, they provide limited, formulation-specific information on short-term tolerability rather than definitive evidence of the safety or metabolic benefits of isolated piceatannol.

Moreover, additional support for the short-term tolerability of piceatannol is provided by two randomized crossover trials in healthy young men receiving 10 mg/day for seven days. Although these studies were designed to evaluate endothelial function and fat oxidation rather than safety, no supplementation-related adverse events or tolerability concerns were reported. However, the small sample sizes, short intervention periods, and absence of comprehensive safety assessments limit these observations to the lack of reported major short-term safety signals under the specific conditions investigated [130,131].

Collectively, the available human investigations provide preliminary information regarding the short-term tolerability of purified piceatannol and selected piceatannol-containing botanical preparations under the specific conditions examined [82–84,129–131]. However, these interventions should not be considered pharmacologically interchangeable, and the absence of major adverse events following administration of a botanical extract does not independently establish the safety of purified piceatannol at an equivalent nominal dose. Furthermore, the total extract dose, quantified piceatannol content, and accompanying phytochemical constituents must be considered when interpreting formulation-specific safety findings. Existing trials have enrolled relatively small numbers of participants, have been of short duration, and have primarily included healthy individuals or mildly overweight adults. Consequently, the available clinical evidence is insufficient to characterize the safety of long-term supplementation, dose escalation, dose–toxicity relationships, or reproductive and developmental exposure. Important uncertainties also remain regarding drug–supplement interactions, particularly in individuals receiving multiple medications, and the pharmacokinetics and safety of piceatannol in patients with hepatic or renal impairment. Moreover, safety has not been adequately established in clinically relevant populations, including individuals with obesity, T2DM, MASLD, cardiovascular disease, and older adults, who may have multiple comorbidities and receive concomitant pharmacotherapies. Therefore, the absence of major adverse events in the available small, short-duration trials should be interpreted only as a lack of reported major short-term safety signals under the investigated doses, formulations, and participant characteristics, rather than evidence of an established favorable safety profile. Future investigations should incorporate systematic adverse-event monitoring, comprehensive laboratory safety assessments, dose-escalation protocols, evaluation of potential drug–supplement interactions, and longer follow-up periods, particularly in vulnerable populations and individuals with obesity-associated metabolic disorders.

8. Translational Challenges, Future Directions, and Clinical Perspectives

8.1. Bridging Experimental Evidence and Clinical Practice

Over the past decade, an expanding body of experimental research has identified piceatannol as a potentially promising naturally occurring stilbene for investigating obesity-

associated metabolic dysfunction. As discussed in the preceding sections, mechanistic studies have reported that piceatannol could modulate multiple interconnected pathways involved in adipogenesis, adipose tissue inflammation, oxidative stress, mitochondrial dysfunction, lipid metabolism, and insulin signaling [82,129,131–133]. Animal investigations have additionally reported changes in selected obesity-related metabolic outcomes; however, these physiological observations do not establish that the molecular mechanisms identified in cellular experiments are responsible for the effects observed in vivo. In particular, the available evidence generally lacks integrated assessments of tissue exposure, molecular target engagement, pathway-specific perturbation, and causal mediation linking the proposed mechanisms to the measured metabolic outcomes. Moreover, the magnitude, consistency, and reproducibility of these effects remain uncertain because of substantial differences in experimental models, administered doses, treatment durations, and outcome measurements. Importantly, preclinical investigations have also examined piceatannol beyond obesity research, with potentially beneficial biological effects reported in selected experimental models of T2DM, MASLD, dyslipidemia, cardiovascular dysfunction, intestinal inflammation, colorectal cancer, and other metabolic and inflammatory disorders. Although these observations suggest that piceatannol may influence molecular pathways shared by several pathological conditions, the heterogeneity of experimental approaches and limited independent replication of certain findings preclude definitive conclusions regarding the consistency of its biological effects across different disease models. Consequently, its potential biological activity may extend beyond body weight regulation to several obesity-related cardiometabolic complications. Taken together, the breadth of available experimental observations and the biological plausibility of the proposed mechanisms provide a preliminary rationale for further translational investigation of piceatannol. Nevertheless, these findings should be interpreted as hypothesis-generating rather than conclusive evidence of reproducible therapeutic efficacy [79,115,122].

Early clinical investigations suggest that short-term oral piceatannol supplementation is feasible and has not raised major tolerability concerns under the conditions examined [82,129]. However, favorable cardiometabolic findings from the principal randomized trial were restricted to a small subgroup of overweight men, have not been independently replicated, and may be influenced by multiple comparisons. Although selected molecular biomarker changes have also been reported, these findings do not establish clinically meaningful metabolic or anti-obesity efficacy. Although the available randomized controlled trials provide valuable proof-of-concept evidence, their relatively small sample sizes, short intervention periods, heterogeneous study populations, and reliance on surrogate metabolic endpoints preclude definitive conclusions regarding therapeutic efficacy. Consequently, adequately powered, multicenter randomized controlled trials involving individuals with obesity and related metabolic disorders are now required to determine whether the promising experimental findings translate into clinically meaningful long-term benefits [82,129–133].

Further characterization of piceatannol pharmacokinetics and formulation-dependent exposure is necessary before its potential clinical relevance can be adequately evaluated. Although piceatannol and resveratrol may differ in their metabolic pathways and systemic exposure under particular experimental conditions, the available evidence does not establish a consistent pharmacokinetic advantage for piceatannol. Its clinical translation remains constrained by poor aqueous solubility, extensive phase II metabolism, and insufficient characterization of target-tissue exposure [35,72]. Advances in formulation science, including nanoformulations, lipid-based delivery systems, and cyclodextrin inclusion complexes, provide potential approaches for addressing the physicochemical and absorption-related limitations of piceatannol [35,52–54]. However, most available findings concern in vitro

formulation characteristics or preclinical pharmacokinetics, and evidence demonstrating improved human systemic exposure, target-tissue delivery, or clinically meaningful metabolic benefits remains insufficient. Future clinical studies should therefore employ standardized formulations, comprehensive pharmacokinetic characterization, and evidence-based dose optimization to improve the reproducibility and comparability of clinical outcomes.

An additional translational challenge concerns the distinction between purified piceatannol and piceatannol-rich botanical preparations. Although both approaches may be relevant to future nutraceutical development, they represent pharmacologically distinct interventions. Purified piceatannol permits more direct evaluation of compound-specific dose–response relationships, pharmacokinetics, and biological target engagement, whereas botanical extracts introduce additional variability arising from phytochemical composition, extraction procedures, and interactions among constituents. Such interactions may influence gastrointestinal absorption, metabolism, systemic exposure, and biological responses, although their contribution requires direct experimental confirmation. Therefore, evidence obtained with botanical extracts should not be extrapolated directly to purified piceatannol, or vice versa, without appropriate comparative investigations. Future clinical trials should clearly report the purity of isolated piceatannol or, for botanical preparations, the botanical source, extraction and standardization procedures, phytochemical composition, total extract dose, and quantified piceatannol content. Direct comparative studies using equivalent piceatannol doses would be particularly valuable for distinguishing compound-specific pharmacological effects from those associated with the broader botanical matrix. Such investigations should also characterize major coexisting constituents, including scirpusin B where present, and assess whether differences in pharmacokinetics, biological activity, or tolerability persist when purified piceatannol and botanical extracts are compared at equivalent piceatannol doses. Until these comparisons are available, evidence obtained with botanical preparations should remain distinct from compound-specific evidence in assessments of anti-inflammatory activity, metabolic efficacy, and safety.

Although favorable metabolic effects of piceatannol have been reported in several preclinical investigations, the overall evidence remains heterogeneous, and the reproducibility of individual findings across comparable experimental conditions has not been adequately established. Considerable differences in animal models, treatment durations, dosing regimens, formulations, and outcome measures further complicate the interpretation and comparison of experimental results [32,115,122].

While this diversity has expanded understanding of the biological activities of piceatannol, it also complicates comparisons across studies and limits identification of optimal therapeutic strategies. Future preclinical investigations should therefore prioritize standardized experimental methodologies, clinically relevant disease models, harmonized outcome measures, and direct comparisons with established anti-obesity pharmacotherapies or well-characterized dietary bioactive compounds. Such studies would facilitate objective evaluation of the relative therapeutic potential of piceatannol and strengthen the translational framework for subsequent clinical trials.

The limited available clinical studies have not reported major short-term safety signals under the investigated conditions; however, their small sample sizes, short durations, and incomplete safety assessments preclude conclusions regarding the overall safety of piceatannol [82,84,129]. Because obesity and associated metabolic disorders generally require long-term management, future investigations should establish the safety of prolonged supplementation, characterize dose-dependent toxicity, and systematically evaluate potential interactions with conventional pharmacotherapies, particularly in patients with multiple comorbidities or concomitant medications. At the current stage of evidence, research should prioritize direct assessment of pharmacokinetic exposure, molecular target engagement,

and reproducible metabolic outcomes; exploratory multi-omics analyses and precision nutrition approaches may be considered only in subsequent investigations if consistent piceatannol-specific biological and clinical responses are established.

Taken together, the available evidence supports further investigation of piceatannol as an experimental bioactive compound with potential metabolic relevance. However, the current evidence base remains dominated by cellular investigations and a relatively limited number of heterogeneous animal studies, while human trials have primarily assessed short-term surrogate outcomes. Therefore, piceatannol should not yet be regarded as a clinically validated intervention for obesity-associated metabolic dysfunction. Future research should prioritize independent replication of functional effects in relevant animal models, characterization of exposure–response relationships, direct verification of proposed molecular targets, standardized formulations, and adequately powered randomized clinical trials evaluating clinically meaningful outcomes. These investigations are necessary to determine whether the biological activities observed in experimental systems have reproducible therapeutic relevance in humans.

8.2. Future Research Priorities

8.2.1. Expanding Clinical Evidence

Despite encouraging proof-of-concept findings, the current clinical evidence remains insufficient to establish the therapeutic efficacy of piceatannol in obesity and related metabolic disorders. Future research should therefore prioritize adequately powered, multicenter randomized controlled trials employing standardized formulations, evidence-based dosing strategies, and longer intervention periods to evaluate the durability of metabolic benefits and establish long-term safety.

Future studies should also recruit more diverse populations, including participants of different sexes, age groups, ethnic backgrounds, and geographic regions, to improve the generalizability of clinical findings. Although interindividual differences in genetic background, dietary habits, lifestyle, and gut microbiota composition may influence piceatannol exposure or biological responses, their relevance remains insufficiently characterized. Initial clinical investigations should therefore prioritize reproducible efficacy and safety outcomes before attempting microbiome-based responder profiling or individualized supplementation strategies.

Another important priority is the evaluation of piceatannol across different obesity phenotypes and obesity-associated metabolic disorders. Rather than relying solely on body mass index, future clinical trials should incorporate comprehensive metabolic phenotyping to identify patient populations most likely to benefit from intervention. Particular emphasis should be placed on individuals with metabolic syndrome, T2DM, and MASLD, where the anti-inflammatory, antioxidant, and insulin-sensitizing properties of piceatannol may have the greatest clinical relevance.

Finally, future trials should incorporate clinically meaningful endpoints beyond body weight, including body composition, visceral adiposity, insulin sensitivity, hepatic fat content, inflammatory biomarkers, adipokine profiles, and patient-reported outcomes. Such comprehensive and rigorously designed clinical investigations will be essential for determining whether the promising experimental evidence can ultimately be translated into meaningful therapeutic benefits for patients with obesity and its associated metabolic disorders.

8.2.2. Optimization of Dose, Formulation and Bioavailability

Before the clinical applicability of piceatannol can be considered, its efficacy and safety must be established, alongside adequate characterization of its pharmacokinetic properties and formulation-dependent exposure. Although experimental investigations have

identified differences between piceatannol and resveratrol in selected pharmacokinetic parameters, the available evidence does not establish consistently greater metabolic stability or superior oral bioavailability for piceatannol under comparable conditions. Its relatively poor aqueous solubility, extensive phase II metabolism, and insufficiently characterized target-tissue exposure remain important limitations to achieving consistent and pharmacologically relevant exposure following oral administration. Consequently, future research should prioritize the establishment of evidence-based dosing regimens through comprehensive dose–response studies and detailed pharmacokinetic/pharmacodynamic analyses to characterize dose–exposure relationships and identify dosing regimens suitable for subsequent clinical evaluation. Such investigations should distinguish systemic exposure to unconjugated piceatannol from exposure to its circulating metabolites and determine whether experimentally achievable concentrations are sufficient to produce relevant biological effects in target tissues. In this context, the micromolar concentrations employed in selected cell-culture investigations (approximately 5–30 μM, with higher concentrations in some studies) should be interpreted cautiously, since corresponding concentrations of unconjugated piceatannol have not been established in human circulation, as discussed in Section 3.4. This exposure gap limits direct extrapolation of the reported in vitro effects to clinically achievable conditions.

Further advances in formulation science may contribute to addressing the physicochemical and pharmacokinetic limitations of piceatannol, although their clinical relevance remains to be established. Future investigations should continue to evaluate innovative delivery systems, including nanoformulations, self-emulsifying drug delivery systems, and cyclodextrin-based inclusion complexes. Importantly, piceatannol-specific findings should be distinguished from evidence extrapolated from resveratrol and other polyphenols, while improvements in in vitro solubility, dissolution, or release characteristics should not be interpreted as direct evidence of enhanced oral bioavailability. Although selected preclinical investigations have reported improved absorption following administration of formulated piceatannol, these findings cannot be directly generalized to human pharmacokinetics. Furthermore, increased systemic exposure, including a higher plasma area under the concentration–time curve (AUC), does not necessarily establish increased concentrations of pharmacologically active compounds in metabolically relevant tissues, molecular target engagement, or improved clinical outcomes. Accordingly, direct comparisons among different formulation approaches under standardized experimental conditions, incorporating quantitative pharmacokinetic measurements, tissue-distribution assessments, and relevant pharmacodynamic endpoints, are needed to identify delivery strategies with demonstrable translational potential.

In addition to pharmaceutical formulations, greater attention should be given to the influence of dietary factors on piceatannol bioavailability. Future studies should investigate the effects of food matrices, meal composition, and interactions with other dietary bioactive compounds on absorption, metabolism, and biological activity. Such investigations may inform the design and characterization of piceatannol-containing functional foods or nutraceutical preparations, although their clinical efficacy, long-term safety, and practical applicability remain to be established.

Overall, characterization of dose–exposure relationships, formulation properties, and bioavailability represents an important research priority for determining whether piceatannol warrants further clinical investigation. However, future pharmacokinetic/pharmacodynamic investigations should extend beyond maximizing systemic exposure to the unconjugated parent compound and consider the potential biological contributions of its phase II metabolites. In particular, studies comparing the activity of individual glucuronide, sulfate, and O-methylated derivatives with that of piceatannol, together with investigations

of potential tissue-specific enzymatic deconjugation, may help identify the molecular species responsible for its effects in vivo. Such evidence would support more biologically informed formulation development, dose optimization, and interpretation of clinical outcomes.

8.2.3. Interindividual Variability and Exploratory Biomarker Research

Interindividual variability in piceatannol absorption, metabolism, and biological responses remains insufficiently characterized. Although genetic background, metabolic status, dietary habits, and gut microbiota composition may influence the pharmacokinetics and biological activity of dietary polyphenols, direct piceatannol-specific evidence identifying reproducible predictors of clinical responsiveness is currently lacking. Consequently, the immediate research priority should be to establish whether piceatannol produces consistent and clinically meaningful metabolic effects under standardized intervention conditions before attempting to distinguish responder subgroups or develop individualized supplementation strategies.

Exploratory biomarker investigations may be incorporated into appropriately designed pharmacokinetic and clinical studies, particularly to characterize circulating piceatannol metabolites, biological exposure, and molecular target engagement. However, comprehensive multi-omics profiling, including metabolomics, transcriptomics, proteomics, and lipidomics, should be regarded as an optional hypothesis-generating approach rather than an essential prerequisite for clinical translation. Any candidate biomarkers would require independent replication and validation before being used to predict treatment response or guide intervention selection.

Similarly, microbiome-based responder profiling and precision nutrition strategies remain premature in the absence of reproducible piceatannol-specific clinical efficacy and validated exposure–response relationships. Future research should first determine whether variation in gut microbiota composition or host metabolic characteristics is associated with measurable differences in piceatannol pharmacokinetics or biological effects. Only after such associations have been independently confirmed would more individualized intervention approaches warrant systematic investigation.

8.2.4. Exploratory Combination Studies and Interaction Assessment

The potential interactions between piceatannol and established obesity-management interventions represent an exploratory research question rather than a clinically supported therapeutic strategy. Given the multifactorial pathophysiology of obesity, future preclinical investigations could examine whether piceatannol interacts with dietary interventions, physical activity, pharmacological treatments, or other bioactive compounds. However, additive or synergistic metabolic effects, improved clinical outcomes, and the safety of such combinations have not been established. Accordingly, investigations should initially prioritize appropriate experimental models, pharmacokinetic and pharmacodynamic interaction assessments, and relevant safety endpoints before considering clinical combination studies.

One promising area of investigation is the evaluation of piceatannol supplementation in combination with healthy dietary patterns, particularly the Mediterranean diet, which is rich in polyphenols, unsaturated fatty acids, dietary fiber, and other bioactive constituents known to improve metabolic health. Similarly, future investigations could evaluate whether combining piceatannol with structured exercise programs or evidence-based weight-loss interventions produces additional changes in adiposity, insulin sensitivity, mitochondrial-related biomarkers, or cardiometabolic outcomes compared with either intervention alone. Whether such combinations improve adipose-tissue function remains to be established through direct assessment of relevant structural, endocrine, immunological, and metabolic endpoints.

The potential use of piceatannol alongside established anti-obesity pharmacotherapies, including GLP-1 receptor agonists, remains entirely hypothetical. At present, the available evidence does not establish additive or synergistic metabolic effects, improved weight-loss maintenance, reduced medication requirements, or fewer treatment-related adverse events following such combinations. Accordingly, clinical combination trials would be premature before the independent efficacy, pharmacokinetics, and safety of piceatannol have been adequately characterized. If a sufficiently strong experimental rationale emerges, initial investigations should evaluate potential pharmacokinetic and pharmacodynamic interactions and safety in appropriate preclinical models before considering controlled human studies.

Combinations of piceatannol with other dietary polyphenols, including resveratrol, quercetin, epigallocatechin gallate (EGCG), and curcumin, represent another exploratory research question rather than an established strategy for enhancing metabolic efficacy. Although these compounds influence some overlapping molecular pathways, such mechanistic similarities do not demonstrate additive or synergistic effects when administered together. Direct piceatannol-specific combination studies assessing interaction effects, pharmacokinetics, safety, and relevant metabolic outcomes are required before claims regarding enhanced efficacy, dose reduction, or clinical applicability can be justified.

8.2.5. Addressing Remaining Mechanistic Gaps

Despite substantial advances in understanding the biological activities of piceatannol, several important mechanistic questions remain unresolved. Future research should move beyond describing downstream biological effects and focus on identifying the primary molecular targets through which piceatannol initiates its diverse metabolic and anti-inflammatory actions. A more comprehensive understanding of these upstream regulatory mechanisms will help distinguish direct pharmacological effects from secondary adaptive responses and facilitate the development of more targeted therapeutic strategies. In particular, the contribution of Syk inhibition to the anti-inflammatory and metabolic effects of piceatannol warrants further investigation [112–115]. Although piceatannol has been characterized as a Syk inhibitor in selected experimental systems, its target selectivity and the relevance of this mechanism to obesity-associated adipose tissue dysfunction remain uncertain [112–115]. Future studies should incorporate direct assessments of Syk activity, genetic silencing or deletion, and comparisons with more selective Syk inhibitors to distinguish Syk-dependent effects from alternative mechanisms. Such investigations should also determine whether Syk inhibition occurs at concentrations achievable in metabolically relevant tissues following oral piceatannol administration [112–115].

A central priority is to establish whether molecular pathways identified in cultured adipocytes or other cellular systems causally mediate the physiological effects observed in animal models. Future investigations should combine quantitative measurements of piceatannol and its major metabolites in relevant tissues with direct assessments of target engagement and pathway activity at biologically achievable concentrations. Where feasible, pathway-specific pharmacological inhibition, genetic silencing or deletion, and appropriate rescue experiments should be employed to determine whether the proposed molecular targets are necessary for the observed responses. These approaches should be integrated with tissue-specific functional measurements, including insulin-stimulated glucose uptake, hepatic glucose production, lipid synthesis and oxidation, and other relevant metabolic flux endpoints. Such studies would help distinguish direct molecular actions from secondary adaptive changes accompanying reductions in adiposity or improvements in systemic metabolic parameters. Importantly, concordance between cellular signaling responses and animal metabolic outcomes should be considered hypothesis-supporting rather than

definitive evidence of mechanistic mediation unless the relevant causal relationships have been experimentally demonstrated.

Further investigation is also required to elucidate the tissue-specific actions of piceatannol across metabolically active organs, including adipose tissue, liver, skeletal muscle, pancreas, and the gastrointestinal tract. Given the complex pathophysiology of obesity, future studies should characterize how piceatannol influences inter-organ communication and whether its therapeutic effects result from coordinated regulation of multiple tissues rather than isolated actions within individual organs. Particular attention should be directed toward the mechanisms governing mitochondrial remodeling and metabolic flexibility, as improvements in mitochondrial function may represent a central mechanism underlying the broad metabolic benefits observed in experimental studies.

Another important priority is the characterization of the interactions between piceatannol and the immune microenvironment of adipose tissue. Future studies should distinguish circulating inflammatory responses from liver- and adipose-specific inflammatory changes and assess both cytokine mRNA and protein concentrations where appropriate. Particular attention should be given to adipose-tissue immune-cell infiltration, macrophage abundance and phenotype, inflammasome activation, and histological inflammation. These outcomes should be evaluated using complementary methods, including tissue immunohistochemistry, flow cytometry, cytokine protein assays, and appropriate pathway-specific measurements. Importantly, changes in macrophage-associated markers alone should not be considered definitive evidence of functional macrophage polarization or immune-cell remodeling. Future investigations should also clarify whether piceatannol influences adipocyte–macrophage communication in vivo and whether these changes contribute causally to metabolic outcomes. Where feasible, genetic or pharmacological perturbation of the implicated inflammatory pathways, together with direct assessment of tissue exposure to piceatannol and its metabolites, would strengthen mechanistic interpretation. Likewise, increasing attention should be given to the role of inter-organ signaling pathways, particularly the adipose–gut and adipose–liver axes, which are increasingly recognized as major contributors to systemic inflammation, insulin resistance, and metabolic dysfunction.

A particularly important research priority is the direct assessment of adipose-tissue function in vivo using complementary structural, vascular, immunological, endocrine, and metabolic endpoints. Future investigations should evaluate adipose fibrosis and extracellular-matrix remodeling through collagen deposition, extracellular-matrix-associated proteins, and relevant histological measurements; vascularization and tissue hypoxia through vascular density, angiogenic markers, and hypoxia-related assessments; and immune-cell composition through appropriate immunophenotyping approaches. The endocrine effects of piceatannol should be investigated through measurements of adipokine secretion, particularly adiponectin and leptin, while adipocyte turnover and adipose-tissue expandability should be evaluated using suitable longitudinal and cell-lineage approaches. Furthermore, depot-specific insulin responsiveness should be assessed using functional measurements of insulin-stimulated glucose uptake and downstream signaling in visceral and subcutaneous adipose tissue. These complementary investigations would help determine whether changes in adiposity, adipocyte morphology, and inflammatory signaling are accompanied by genuine improvements in adipose-tissue function, rather than representing isolated experimental responses.

Another critical research question concerns the potentially dual metabolic consequences of sustained inhibition of adipogenesis. Future studies should determine whether piceatannol differentially affects physiological adipocyte recruitment and pathological adipocyte hypertrophy, particularly across subcutaneous and visceral adipose depots. Longitudinal investigations should assess adipocyte hyperplasia and hypertrophy, adipose-

tissue expandability, circulating nonesterified fatty acids, lipid spillover, and ectopic lipid accumulation in the liver and skeletal muscle. These measurements should be integrated with depot-specific insulin responsiveness and systemic metabolic outcomes to establish whether suppression of adipogenic differentiation is associated with beneficial metabolic adaptations or unintended impairment of lipid-buffering capacity. Particular attention should be given to treatment duration, nutritional status, and the potential consequences of chronic exposure.

Finally, future studies should address biological variables that remain largely unexplored, including circadian regulation and sex-specific responses to supplementation. Circadian rhythms influence energy metabolism, inflammatory signaling, and mitochondrial function, while sex-related differences in hormone profiles and adipose tissue biology may substantially modify therapeutic responsiveness. Incorporating these factors into future experimental and clinical investigations will improve mechanistic understanding, enhance translational relevance, and help determine whether circadian and sex-related factors influence the experimentally observed biological responses to piceatannol, without presupposing the feasibility or effectiveness of personalized clinical interventions. Figure 4 summarizes the translational framework of piceatannol, integrating current evidence from natural dietary sources, pharmacokinetic characteristics, mechanistic in vitro studies, preclinical animal models, randomized clinical trials, and the principal challenges and future directions for its clinical application in obesity and metabolic disease.

8.3. Piceatannol Versus Resveratrol: Critical Appraisal of Comparative Experimental and Clinical Evidence

8.3.1. Structural and Pharmacokinetic Considerations

Piceatannol and resveratrol are structurally related stilbenes that differ by an additional hydroxyl group in piceatannol, resulting in a catechol moiety. This structural distinction can influence redox chemistry, molecular interactions, and metabolic transformation, but it does not independently establish greater biological or therapeutic efficacy [32,72]. Selected direct comparative chemical investigations have reported differences in radical-scavenging activity; however, the direction and magnitude of these differences depend on the assay, reaction conditions, and endpoints evaluated. Consequently, chemical antioxidant potency should not be equated with superior antioxidant or anti-inflammatory activity in intact biological systems.

Both compounds undergo extensive metabolism following oral administration, and their pharmacokinetic profiles are influenced by species, administered dose, formulation, route, sampling conditions, and the relative abundance of unconjugated and conjugated metabolites [71,72,75]. Although differences in metabolic stability or systemic exposure have been reported in individual investigations, the available evidence does not establish a reproducible pharmacokinetic advantage for piceatannol under standardized, clinically relevant conditions. Furthermore, piceatannol can be formed through metabolism of resveratrol, but the extent to which this pathway contributes to the biological effects of resveratrol in humans remains uncertain.

Accordingly, piceatannol and resveratrol should be regarded as structurally related compounds with potentially distinct pharmacological profiles rather than ranked according to presumed pharmacokinetic or therapeutic superiority. Further head-to-head pharmacokinetic studies should compare equivalent administration conditions, characterize parent compounds and major metabolites, and assess systemic and target-tissue exposure. The principal physicochemical, pharmacokinetic, biological, and translational characteristics of piceatannol and resveratrol are summarized in Table 3, with explicit distinction between established chemical properties, direct experimental comparisons, and indirect observations

from independent investigations. Importantly, the available evidence does not establish consistent pharmacokinetic, pharmacological, or therapeutic superiority of either stilbene, and their comparative clinical efficacy and safety remain undetermined.

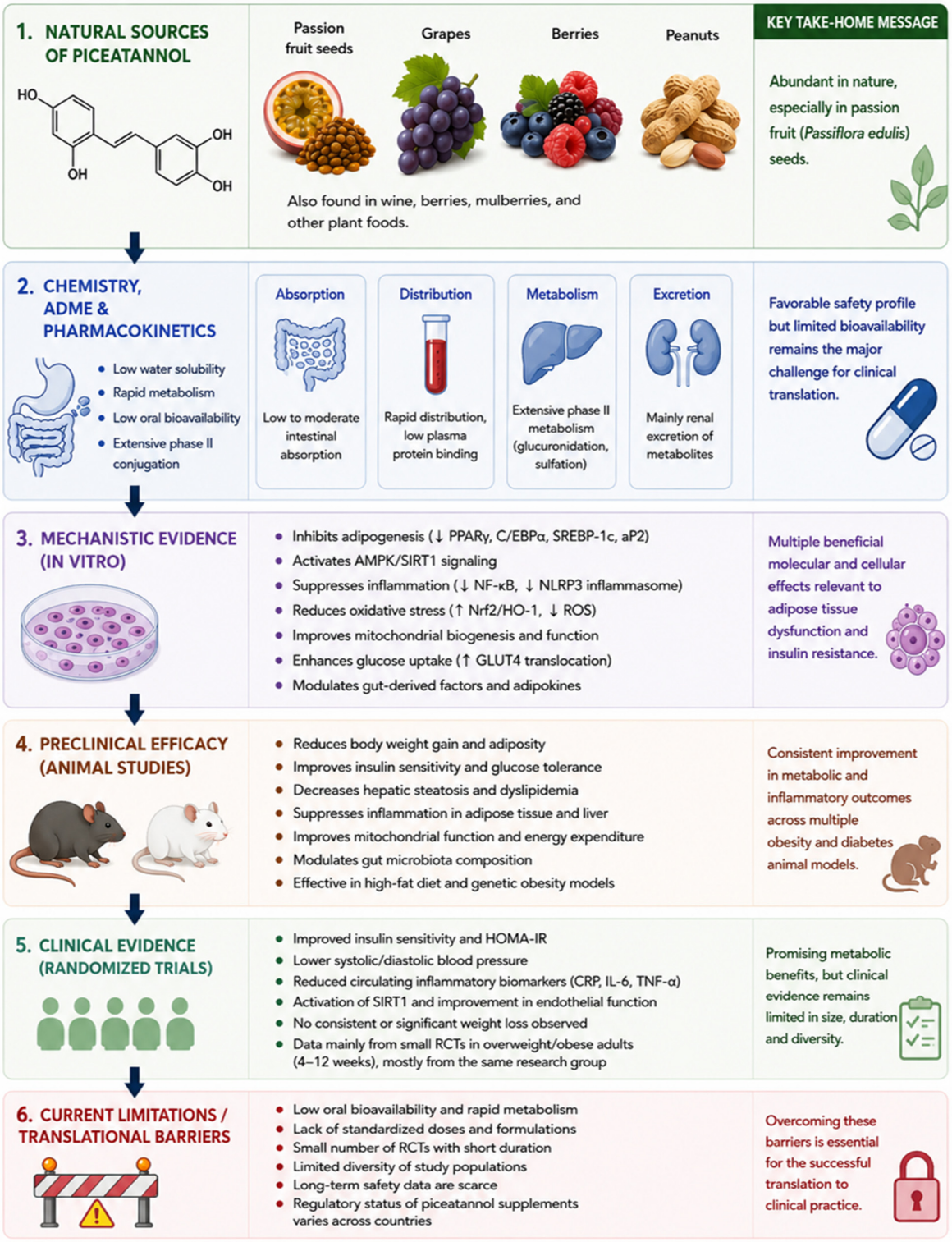


Figure 4. Evidence levels, translational limitations, and future research priorities for piceatannol in obesity-associated metabolic dysfunction.

Table 3. Physicochemical Characteristics and Available Comparative Evidence for Piceatannol and Resveratrol: Established Properties, Experimental Observations, and Evidence Gaps *#.

Characteristic	Resveratrol	Piceatannol	Comparative Evidence Type and Interpretation	Representative References
Chemical structure	3,5,4′-Trihydroxystilbene; three hydroxyl groups	3,3′,4,5′-Tetrahydroxystilbene; four hydroxyl groups	Established structural distinction; does not establish biological superiority	[43,48,49,72]
Molecular formula	$C_{14}H_{12}O_3$	$C_{14}H_{12}O_4$	Established chemical property	[43,45]
Molecular weight (g/mol)	228.24	244.24	Established chemical property	[43,45]
Catechol moiety	Absent	Present	Established structural distinction that may influence redox chemistry and metabolism	[48,49]
Antioxidant activity	Radical-scavenging activity reported in chemical assays	Greater radical-scavenging activity reported in selected comparative assays	Assay-dependent chemical evidence; no established overall superiority in biological antioxidant efficacy	[48,49,115]
Redox behavior	Phenoxyl radical formation and stabilization depend on reaction conditions	Additional hydroxyl group may influence electron transfer and radical stabilization	Chemical and mechanistic evidence; not a direct measure of antioxidant efficacy in vivo	[48,49]
Aqueous solubility	Poor	Poor	Physicochemical evidence; both compounds present formulation challenges	[52]
Lipophilicity	Moderately lipophilic	Moderately lipophilic; reported logP approximately 2.6	Compound-specific physicochemical measurements; not evidence of superior tissue penetration	[50,51]
Chemical stability in aqueous media	Susceptible to oxidative and environmental degradation, depending on experimental conditions	Catechol moiety may increase susceptibility to oxidation under particular aqueous and oxygen-exposed conditions	Chemical stability depends on pH, oxygen, temperature, light, and experimental medium; no universal comparative ranking is established	[53,72]
Intestinal absorption	Absorption followed by extensive presystemic metabolism	Absorption followed by extensive presystemic metabolism	Compound-specific pharmacokinetic evidence; direct comparative absorption differences remain uncertain	[71,72]
Tissue distribution	Distribution to multiple tissues reported experimentally	Distribution to liver, adipose tissue, skeletal muscle, kidney, and cardiovascular tissues reported experimentally	Primarily compound-specific evidence; tissue detection does not establish equivalent or superior target-tissue exposure	[72,75]
Major metabolic pathways	Glucuronidation, sulfation, and methylation	Glucuronidation, sulfation, and COMT-mediated O-methylation	Established metabolic pathways; differences do not establish greater metabolic stability	[72,75,76]
Metabolic stability and elimination in vivo	Undergoes extensive phase II metabolism, including glucuronidation and sulfation	Undergoes extensive phase II metabolism, including glucuronidation, sulfation, and O-methylation; systemic persistence depends on the administered dose, route, and measured analytes	Chemical oxidation susceptibility does not predict enzymatic metabolic stability, systemic clearance, or elimination half-life; available evidence does not establish a consistent comparative advantage	[71,72,75,81]
Systemic exposure	Exposure depends on dose, route, formulation, and measured analytes	Exposure depends on dose, route, formulation, and measured analytes	Available evidence insufficient for a general ranking of plasma exposure or bioavailability	[72,75]
Absolute oral bioavailability	Limited	Limited	Compound-specific pharmacokinetic evidence; standardized head-to-head human data are insufficient	[71,72]
Advanced delivery systems	Nanotechnology-based formulations investigated	Nanoemulsions, liposomes, polymeric nanoparticles, cyclodextrin complexes, and self-emulsifying systems investigated	Formulation-specific evidence; no established comparative clinical delivery advantage	[52,54,90,91]

Table 3. *Cont.*

Characteristic	Resveratrol	Piceatannol	Comparative Evidence Type and Interpretation	Representative References
Adipogenic differentiation	Inhibition reported in experimental cellular systems	Inhibition reported in experimental cellular systems; greater suppression of selected endpoints in a matched comparison	Direct cellular comparison by Park et al. [117]; findings limited to the investigated model and conditions	[115–117]
Glucose metabolism	Glucose-regulatory effects reported in experimental and clinical investigations	Glucose-regulatory effects reported in experimental and limited clinical investigations	Selected direct animal comparisons and indirect evidence; no established overall superiority in insulin sensitivity or glycemic control	[82,123,127,128]
Anti-inflammatory activity	Modulation of inflammatory pathways reported in experimental systems	Modulation of inflammatory pathways reported in experimental systems; limited tissue-specific animal evidence	Predominantly separate experimental investigations; no established superiority in systemic or adipose-tissue inflammation	[34,48,123,133]
Mitochondrial function	Effects on mitochondrial signaling and oxidative metabolism reported	Effects on mitochondrial signaling and oxidative metabolism reported	Predominantly model-specific evidence; insufficient direct comparisons for a general ranking	[35,115,129]
Preclinical metabolic efficacy	Selected favorable metabolic outcomes reported in animal models	Selected favorable metabolic outcomes reported in animal models, with heterogeneous weight- and adiposity-related findings	Limited direct comparisons; overall efficacy cannot be ranked across different models and endpoints	[77,122–128]
Clinical evidence	Larger clinical literature, including randomized trials and meta-analyses; findings vary by population and endpoint	Limited clinical trials reporting selected metabolic outcomes, with inconsistent or population-specific effects	No direct head-to-head clinical trial; comparative clinical efficacy and safety cannot be established	[82,83,130,131, 134–137]
Overall translational status	Investigational for obesity-related indications; clinical evidence is more extensive but heterogeneous	Investigational for obesity-related indications; requires further pharmacokinetic, efficacy, and safety evaluation	No demonstrated comparative therapeutic superiority or established clinical safety advantage	[35,72,82]

* **Abbreviations:** COMT, catechol-O-methyltransferase; logP, octanol–water partition coefficient; SNEDDS, self-nanoemulsifying drug delivery systems. # **Notes:** The table compares the physicochemical, pharmacokinetic, biological, and translational characteristics of piceatannol and resveratrol. Direct experimental comparisons are restricted to the specific models, doses, and endpoints investigated, while indirect comparisons do not establish relative efficacy. Greater radical-scavenging activity or favorable metabolic responses do not necessarily indicate superior biological or therapeutic effects. No direct clinical trials have established the comparative efficacy or safety of these compounds in humans.

8.3.2. Comparative Molecular Mechanisms

Piceatannol and resveratrol have been investigated for their effects on several signaling pathways implicated in obesity-associated metabolic dysfunction, including AMPK, SIRT1, NF-κB, Nrf2, and PI3K/Akt. However, similarities or differences in pathway-associated responses reported across independent studies do not establish equivalent or superior molecular activity, particularly when experimental models, concentrations, exposure durations, and outcome measurements differ. Direct comparisons should therefore be interpreted according to the specific experimental conditions and endpoints assessed.

The historical identification of piceatannol as a Syk inhibitor represents an additional pharmacological feature potentially relevant to comparisons with resveratrol [112–114]. However, as discussed in Sections 4.3.3 and 5.3, its limited target selectivity and the absence of direct evidence linking Syk inhibition to improved obesity-associated metabolic outcomes prevent attribution of its anti-inflammatory effects specifically to this pathway. Whether Syk-associated mechanisms contribute to meaningful differences between piceatannol and resveratrol therefore requires direct comparative investigation.

Among the available cellular investigations, Park et al. (2021) reported greater inhibition of selected adipogenic endpoints by piceatannol than by resveratrol in human visceral adipose-derived stem cells under the conditions investigated [117]. These findings support an experimental difference in adipogenic responses within that model but do not establish superior anti-obesity activity. In particular, greater inhibition of adipocyte differentiation should not automatically be interpreted as metabolically advantageous, because physiological adipogenesis contributes to adipose-tissue expandability and appropriate lipid storage.

Selected experimental investigations have also directly compared the two stilbenes in relation to glucose-regulatory, hepatic, oxidative, or inflammatory endpoints [123,127]. Where differences were observed, they should be attributed only to the specific measured outcomes, models, doses, and treatment protocols. Improvements in fasting glucose, glucose tolerance, or surrogate indices of insulin resistance should not be considered interchangeable with directly demonstrated improvements in insulin sensitivity. Similarly, greater radical-scavenging activity in chemical assays does not establish superior cellular antioxidant protection, and changes in hepatic inflammatory markers do not demonstrate generalized systemic or adipose-tissue anti-inflammatory efficacy.

Overall, the available molecular evidence identifies potentially distinct, context-dependent biological responses to piceatannol and resveratrol but does not support a general ranking of their antioxidant, anti-inflammatory, anti-adipogenic, glucose-regulatory, or metabolic activities. Additional head-to-head investigations using matched experimental conditions, appropriate concentration–response analyses, standardized endpoints, and direct assessments of pathway engagement are required to determine whether the observed differences are reproducible and biologically meaningful.

8.3.3. Comparative Therapeutic Efficacy in Experimental Models

Resveratrol and piceatannol have both been investigated in experimental models of obesity and metabolic disease, although the quantity and diversity of available evidence differ considerably between the two compounds. Resveratrol has been evaluated in numerous animal models of diet-induced obesity, metabolic syndrome, T2DM, and MASLD, with beneficial effects reported for selected measures of adiposity, glucose regulation, lipid metabolism, hepatic steatosis, and inflammation. By comparison, the preclinical evidence for piceatannol is substantially more limited and heterogeneous. Individual studies have reported improvements in selected metabolic endpoints, but these observations do not establish broadly reproducible efficacy across experimental models or equivalent effectiveness between the two stilbenes [122,126,138,139].

Comparative experimental investigations have identified differences between piceatannol and resveratrol in selected metabolic endpoints; however, the available animal evidence does not establish consistent superiority of piceatannol or reproducible anti-obesity efficacy across experimental models. Reductions in weight gain, adipose depot mass, or adipocyte hypertrophy have been reported in selected diet-induced and ovariectomy-associated obesity models [77,122,123], whereas other investigations, including studies involving genetically obese animals, have not demonstrated significant reductions in body weight or adiposity [124–127]. Improvements in glucose-regulatory, lipid-related, or hepatic outcomes should therefore be distinguished from direct anti-obesity effects. Furthermore, differences in species, strain, sex, obesity model, administered dose, treatment duration, route, and formulation limit direct comparisons between investigations. Consequently, any apparent advantages of piceatannol over resveratrol should be interpreted as endpoint-specific and model-dependent observations rather than evidence of superior or consistently reproducible metabolic efficacy.

Direct experimental comparisons between piceatannol and resveratrol remain limited. Sun et al. (2025) reported differences in selected glucose-regulatory, hepatic, and adiposity-related endpoints in high-fat diet-fed mice receiving the two compounds under the investigated treatment conditions [123]. These findings provide evidence of endpoint-specific differences within that experimental model but do not establish superior whole-body insulin sensitivity, generalized metabolic efficacy, or greater therapeutic effectiveness across obesity-related disorders. Moreover, differences in experimental dose, systemic exposure, treatment duration, and the physiological relevance of individual endpoints must be considered before drawing broader pharmacological conclusions. Independent replication using standardized comparative protocols is required.

The available preclinical evidence is insufficient to establish comparative therapeutic efficacy between piceatannol and resveratrol. Although individual head-to-head investigations have identified differences in selected experimental endpoints, these observations have not been consistently replicated across independent animal models. Furthermore, indirect comparisons between studies are limited by differences in species, strain, sex, obesity model, administered dose, formulation, treatment duration, route of administration, systemic exposure, and outcome assessment. Consequently, the current evidence does not support conclusions that piceatannol is generally equivalent or superior to resveratrol in anti-obesity or metabolic efficacy.

8.3.4. Comparative Clinical Evidence and Translational Perspectives

The current clinical evidence supporting resveratrol and piceatannol differs substantially in both quantity and maturity. During the past two decades, resveratrol has been extensively investigated in randomized controlled trials involving patients with obesity, metabolic syndrome, T2DM, MASLD, cardiovascular disease, hypertension, and other chronic metabolic disorders. Furthermore, its therapeutic potential has been evaluated in numerous systematic reviews and meta-analyses, providing a comprehensive assessment of its efficacy and safety. Although the reported clinical benefits are generally modest and variable across studies, particularly with respect to body weight reduction, the accumulated evidence supports beneficial effects on insulin sensitivity, glycemic control, endothelial function, inflammation, and several cardiometabolic risk factors [134–137,140,141]. By contrast, the clinical evidence for piceatannol remains at a considerably earlier stage of development and is currently insufficient to define its therapeutic position relative to the much better-characterized parent compound.

The limited randomized clinical studies of piceatannol only provide preliminary evidence of changes in selected cardiometabolic and molecular biomarkers, although findings vary across populations, intervention durations, and measured outcomes. Improvements in selected insulin resistance indices and blood pressure measurements have been reported in particular subgroups, whereas other investigations have observed no significant changes in several metabolic or physiological endpoints [82,129–131]. These findings should be interpreted as exploratory human evidence rather than confirmation of therapeutic efficacy. Furthermore, the absence of adequately powered head-to-head clinical trials prevents conclusions regarding the comparative effectiveness of piceatannol and resveratrol in obesity or related metabolic disorders.

The principal limitation of the available evidence is that no randomized controlled trial has directly compared piceatannol with resveratrol under identical clinical conditions. Consequently, any apparent therapeutic advantage of piceatannol is derived from indirect comparisons between independent studies employing different populations, formulations, treatment durations, and clinical endpoints. Moreover, even if future comparative trials demonstrate statistically greater efficacy for piceatannol, the clinical significance of such

differences will require careful evaluation. Obesity and its associated metabolic disorders are multifactorial conditions in which modest improvements in biochemical or physiological markers do not necessarily translate into meaningful reductions in diabetes progression, cardiovascular risk, hepatic disease, or long-term weight management. Therefore, future comparative studies should evaluate not only statistical superiority but also clinically meaningful improvements in patient-centered outcomes.

Taken together, the available evidence supports continued investigation of piceatannol as a structurally related stilbene with experimentally observed metabolic activities, but its comparative clinical efficacy and safety relative to resveratrol remain unknown. No randomized clinical trial has directly compared the two compounds under matched treatment conditions, and the available human investigations differ substantially in populations, formulations, doses, intervention durations, and measured outcomes. Consequently, indirect comparisons cannot establish clinical equivalence, superiority, or a more favorable safety profile for either compound. Future adequately powered randomized trials employing standardized formulations and clinically meaningful endpoints are required to determine whether any differences observed in experimental systems translate into reproducible benefits in humans.

9. Conclusions

Piceatannol is a naturally occurring stilbene with experimentally observed biological activities relevant to obesity-associated metabolic dysfunction. The evidence synthesized in this review indicates that piceatannol may influence several interconnected processes, including adipocyte differentiation, inflammatory signaling, oxidative responses, and glucose and lipid metabolism. With respect to lipid metabolism, reduced lipid accumulation during adipocyte differentiation should be distinguished from direct effects on mature-adipocyte lipolysis, particularly because some experimental studies demonstrated suppression of lipolysis through autophagy–lysosome-dependent degradation of key lipolytic proteins, while other experimental findings suggest potentially different responses under distinct physiological conditions. Cellular investigations provide mechanistic plausibility and functional evidence for selected biological effects, particularly inhibition of adipogenic differentiation. However, changes in signaling pathways do not necessarily establish direct molecular target engagement or causal mediation. Furthermore, favorable metabolic outcomes observed in animal models do not independently validate the cellular mechanisms proposed to explain them, particularly in the absence of direct measurements of tissue exposure, molecular target engagement, pathway-specific perturbation, and mechanistic mediation.

Animal studies have reported improvements in specific metabolic outcomes, but the limited number of independent investigations, heterogeneous experimental conditions, and incomplete replication restrict conclusions regarding reproducible preclinical efficacy. Selected animal investigations have also reported reductions in hepatic lipid accumulation and improvements in liver-related metabolic endpoints, suggesting potential relevance to MASLD; however, these preliminary findings do not establish efficacy in MASLD or demonstrate that piceatannol directly reverses the underlying hepatic disease processes. Specifically, reductions in body weight or adiposity were reported in only three of the seven animal investigations explicitly evaluating these outcomes, whereas four reported no significant reductions, underscoring the limited, heterogeneous, and model-dependent nature of the available preclinical evidence. Importantly, the available glucose-regulatory findings are based on heterogeneous endpoints, and improvements in fasting glycemia, glucose tolerance, or surrogate indices of insulin resistance, such as HOMA-IR, should not be interpreted as definitive evidence of enhanced whole-body or tissue-specific insulin sensitivity. Direct physiological measurements are required to establish whether the ob-

served glycemic changes reflect improved insulin responsiveness rather than alterations in insulin secretion, hepatic glucose production, or other components of glucose regulation. Similarly, the animal evidence for anti-inflammatory activity remains very limited and largely restricted to selected hepatic cytokine measurements, which do not establish reduced systemic or adipose-tissue inflammation, macrophage remodeling, or in vivo validation of the adipocyte–macrophage mechanisms identified in cellular experiments.

A limited number of direct experimental comparisons have identified differences between piceatannol and resveratrol in selected biological and metabolic endpoints; however, these findings do not establish overall pharmacological superiority, and the absence of head-to-head clinical trials prevents conclusions regarding comparative clinical efficacy or safety. Importantly, the available findings do not establish that piceatannol restores adipose-tissue function in vivo, because key structural, vascular, immunological, endocrine, and depot-specific metabolic endpoints have not been comprehensively investigated. Accordingly, its reported effects on adipogenesis, adiposity, inflammatory markers, and selected metabolic pathways should not be interpreted as evidence of generalized functional improvement in adipose tissue. Moreover, the metabolic consequences of piceatannol-induced inhibition of adipogenesis may be context-dependent, since physiological adipocyte recruitment supports adipose-tissue expandability and appropriate lipid storage, whereas sustained suppression of this process could theoretically compromise lipid-buffering capacity; these potential consequences remain insufficiently investigated in vivo.

The principal limitation remains the gap between experimental biological activity and demonstrated clinical benefit. Preliminary human investigations using purified piceatannol or piceatannol-rich plant extracts have reported changes in selected cardiometabolic and molecular biomarkers; however, the effects of complex extracts cannot be attributed exclusively to piceatannol. Moreover, changes in surrogate biomarkers do not establish clinically meaningful anti-obesity efficacy, and the available trials have not consistently demonstrated improvements in body weight or adiposity. The small sample sizes, short intervention periods, heterogeneous interventions, and absence of independent replication preclude definitive conclusions regarding clinical effectiveness. Pharmacokinetic limitations, particularly extensive first-pass metabolism and variable systemic exposure, further complicate clinical evaluation. Although short-term administration has not revealed major tolerability concerns in the available studies, long-term safety remains insufficiently characterized.

Overall, piceatannol should currently be regarded as an experimental bioactive compound with mechanistic and preliminary preclinical support rather than an established therapeutic intervention for obesity-associated metabolic disorders. Its clinical translation depends on reproducible preclinical evidence, rigorous pharmacokinetic and mechanistic validation, and adequately powered clinical trials assessing meaningful metabolic outcomes and long-term safety. Until these evidence gaps are addressed, its therapeutic potential remains unconfirmed.

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