

REVIEW ARTICLE

Oleanolic acid as an adjunct in type 2 diabetes mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a progressive cardiometabolic disease in which many patients require treatment intensification despite lifestyle intervention and evidence-based pharmacotherapy. Oleanolic acid (OA), a pentacyclic triterpenoid found in olives and other plants, has shown insulin-sensitizing, antioxidant, anti-inflammatory, and hepatometabolic effects in experimental models. **Aim:** This narrative translational review evaluates OA as a potential investigational adjunct in T2DM, with emphasis on formulation-dependent bioavailability, translational limitations, clinical endpoints, safety, and patient relevance. **Methods:** We synthesized mechanistic, preclinical, pharmacokinetic, clinical, regulatory, and trial-registry evidence. As this was not a systematic review or meta-analysis, the evidence was interpreted narratively, with attention to study design, formulation, dose, model validity, comparator use, and potential sources of bias. **Results:** Preclinical studies suggest that OA may influence insulin signaling, hepatic glucose production, oxidative stress, inflammatory pathways, lipid metabolism, and β -cell stress. However, most mechanistic data derive from cell or animal models, often using high doses, short treatment durations, or models with limited human predictability. Human evidence remains limited. PREDIABOLE reported reduced progression from prediabetes to T2DM after long-term intake of OA-enriched olive oil, while BIO-OLTRAD demonstrated measurable systemic exposure after a 30 mg OA dose in functional olive oil. OLTRAD is testing this formulation as an adjunct to metformin-based therapy. **Conclusion:** OA is a plausible investigational adjunct, but clinical efficacy in established T2DM has not been established. Its future value depends on reproducible exposure, clinically meaningful outcomes, long-term safety, compatibility with contemporary therapies, and avoidance of disease-treatment claims unsupported by human trials. **Relevance for Patients:** OA-enriched functional foods may eventually complement, but should not replace, evidence-based diabetes treatment.

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Citation: Günther A, Bednarczyk-Cwynar B, Malinowski M. Oleanolic acid as an adjunct in type 2 diabetes mellitus. *J Clin Transl Res.* 2026;12(4):026220050. doi: 10.36922/JCTR026220050

Received: June 19, 2026

Revised: June 19, 2026

Accepted: July 6, 2026

Published online: July 15, 2026

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Keywords: Oleanolic acid; Type 2 diabetes; Metformin; Insulin resistance; Functional olive oil; Bioavailability; Translational research; Patient-centered outcomes

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic cardiometabolic diseases worldwide and remains a major driver of morbidity, mortality, health-care expenditure, and loss of quality-adjusted life years. Recent global estimates indicate that more than half a billion adults are living with diabetes, with a continued increase projected by 2050; more than 90% of cases are T2DM.¹ Despite major therapeutic progress, durable glycemic control remains difficult for many patients, particularly when insulin resistance, β -cell dysfunction, obesity, cardiovascular disease, chronic kidney disease, treatment burden, and adherence interact over time.

Current standards of care emphasize individualized, person-centered therapy. Drug selection is guided not only by glycemic targets, but also by cardiovascular and kidney comorbidity, weight-management goals, hypoglycemia risk, cost, access, and patient preferences. Metformin remains widely used, while sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, dual incretin agonists, insulin, and other agents are increasingly selected according to risk profile.^{2,3} This expanding therapeutic landscape leaves room for adjunctive strategies only if they are safe, acceptable, affordable, compatible with standard care, and supported by reproducible metabolic benefit.

Oleanolic acid (OA) is a naturally occurring pentacyclic triterpenoid found in several edible and medicinal plants, including olives and olive-derived products.^{4,5} It has attracted interest in metabolic disease because its biological effects intersect with mechanisms relevant to T2DM, including insulin resistance, hepatic glucose production, oxidative stress, low-grade inflammation, lipid metabolism, and pancreatic β -cell vulnerability.⁴⁻⁶ Experimental studies also suggest that OA may complement metformin in diabetic models, supporting the rationale for adjunctive rather than replacement therapy.⁷

Clinical translation of OA is strongly constrained by formulation and bioavailability. OA is hydrophobic and poorly water-soluble, so systemic exposure depends on the delivery matrix, dose, intestinal absorption, and postprandial lipid transport. Early analytical work established methods for measuring OA in human serum⁸

and BIO-OLTRAD later showed that OA administered as functional olive oil produced measurable postprandial serum concentrations and transport through serum albumin and triglyceride-rich lipoproteins.⁹ These findings shift the question from whether OA is active in experimental systems to whether a clinically acceptable formulation can deliver sufficient and reproducible exposure in humans.

Human clinical evidence remains limited but relevant. PREDIABOLE reported that OA-enriched olive oil reduced progression from prediabetes to T2DM during long-term follow-up.¹⁰ However, prevention in prediabetes is not equivalent to adjunctive treatment in established T2DM. Patients with diagnosed T2DM have different metabolic trajectories, background medications, comorbidity burdens, and endpoint expectations. The OLTRAD study therefore represents an important next step because it evaluates OA-enriched functional olive oil as an adjuvant to metformin-based treatment in adults with T2DM.¹¹

This review examines whether OA can be reasonably developed as an adjunctive strategy for T2DM. It integrates mechanistic and preclinical evidence with human bioavailability data, prevention-oriented clinical findings, ongoing adjunctive trial design, safety considerations, and outcomes relevant to clinical practice. The aim is to distinguish evidence-supported conclusions from still-hypothetical claims and to define the research needed before OA-enriched formulations can be considered for diabetes care. The proposed translational pathway from OA-enriched functional olive oil to systemic exposure, tissue-level mechanisms, and patient-relevant endpoints is summarized in [Figure 1](#).

2. Methods for literature synthesis

This article was designed as a narrative translational review rather than a systematic review or meta-analysis. The aim was to integrate evidence across the translational continuum, including molecular and cellular mechanisms, animal models, human pharmacokinetics, clinical prevention data, safety considerations, regulatory positioning, and ongoing adjunctive-therapy trials. The review structure used a predefined narrative framework with explicit search procedures, balanced evidence presentation, and transparent discussion of limitations, consistent with quality principles proposed for narrative

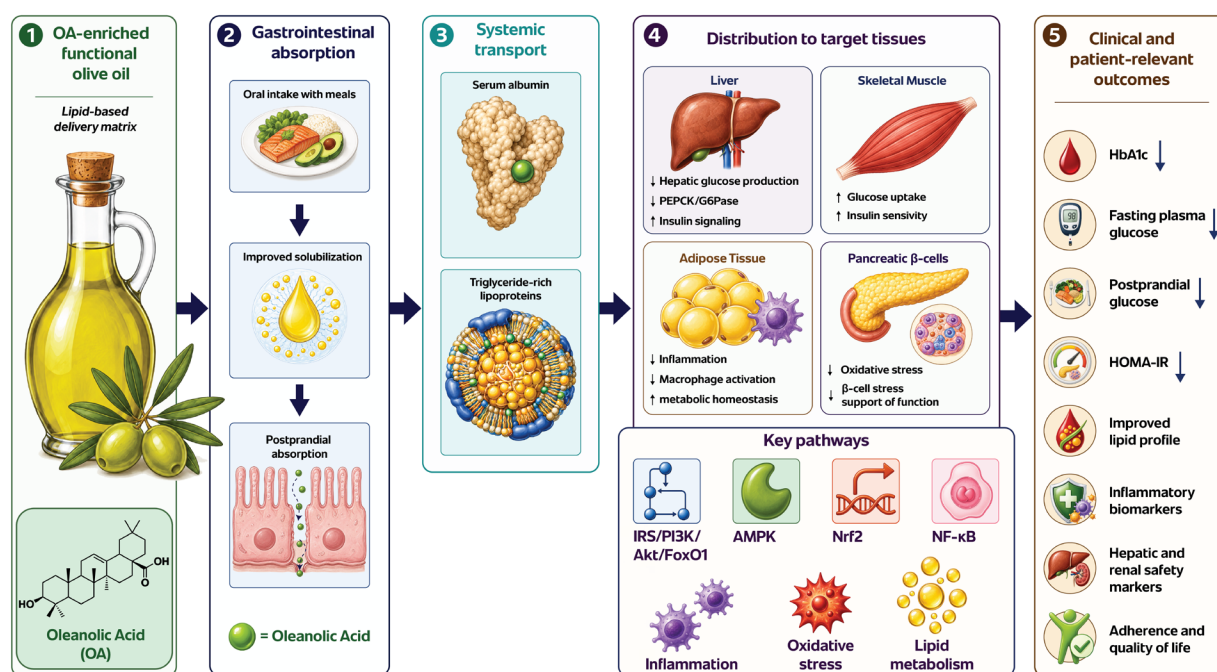


Figure 1. Proposed translational pathway of OA in type 2 diabetes. OA-enriched functional olive oil provides a lipid-based delivery matrix intended to support gastrointestinal solubilization, postprandial absorption, and systemic transport through serum albumin and triglyceride-rich lipoproteins.^{9,12,13} After systemic exposure, OA may distribute to metabolically relevant tissues, including the liver, skeletal muscle, adipose tissue, and pancreatic β-cells. The proposed pathway links formulation-dependent delivery with mechanisms relevant to type 2 diabetes, including insulin signaling, hepatic glucose production, oxidative stress, inflammation, lipid metabolism, β-cell stress, and metabolic homeostasis.^{4–7,14–24} These biological effects should be evaluated against clinically relevant and patient-centered endpoints, including HbA1c, fasting plasma glucose, postprandial glucose, insulin resistance indices, lipid profile, inflammatory biomarkers, hepatic and renal safety markers, adherence, and quality of life.^{25–31} Image created originally by the authors using Adobe Photoshop and Adobe Illustrator.

Abbreviations: Akt: Protein kinase B; AMPK: Adenosine monophosphate-activated protein kinase; FoxO1: Forkhead box O1; G6Pase: Glucose-6-phosphatase; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; IRS: Insulin receptor substrate; NF-κB: Nuclear factor-kappa B; Nrf2: Nuclear factor erythroid 2-related factor 2; OA: Oleanolic acid; PEPCK: Phosphoenolpyruvate carboxykinase; PI3K: Phosphoinositide 3-kinase.

reviews.³² Because quantitative pooling was not planned, the review was not registered with the International Prospective Register of Systematic Reviews (PROSPERO) and was not conducted as a formal systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement; however, PRISMA 2020 principles were used to support transparent reporting of sources and selection procedures.³³

2.1. Search strategy and information sources

A structured literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar from database inception to May 21, 2026. PubMed/MEDLINE was selected for biomedical and clinical literature; Scopus and Web of Science were selected for broader multidisciplinary and citation coverage; and

Google Scholar was used as a supplementary search tool to capture cross-disciplinary formulation, regulatory, and gray-literature records. Clinical trial registries, including ClinicalTrials.gov, were searched to identify ongoing or completed human studies involving OA-enriched formulations in diabetes or prediabetes.¹¹ Reference lists of key reviews and primary studies were screened manually.

Search terms combined the compound, disease context, formulation, and therapeutic strategy. Core terms included “oleanolic acid,” “oleanolic acid-enriched olive oil,” “functional olive oil,” “pentacyclic triterpenes,” “type 2 diabetes,” “T2DM,” “prediabetes,” “insulin resistance,” “metformin,” “SGLT2 inhibitor,” “GLP-1 receptor agonist,” “dual incretin agonist,” “tirzepatide,” “glucose metabolism,” “bioavailability,” “pharmacokinetics,” “Nrf2,” “oxidative stress,” “inflammation,” “hepatic gluconeogenesis,” “beta-

cell,” “endoplasmic reticulum stress,” “unfolded protein response,” “proinsulin,” “dedifferentiation,” “clinical trial,” “PREDIABOLE,” “BIO-OLTRAD,” and “OLTRAD.” Boolean combinations were adapted to each database.

2.2. Eligibility, prioritization, and selection approach

Eligible sources included original mechanistic studies, *in vitro* experiments relevant to insulin signaling or glucose metabolism, animal studies of diabetes or insulin resistance, pharmacokinetic studies, human intervention studies, clinical trial protocols or registry records, systematic reviews, high-quality narrative reviews, and regulatory guidance documents relevant to functional foods, dietary supplements, botanical products, or disease-related health claims.

Evidence was prioritized when it addressed one or more translational questions: whether OA modulates T2DM-relevant mechanisms; whether OA improves glucose homeostasis *in vivo*; whether OA can be delivered with measurable human systemic exposure; whether OA-enriched food matrices affect diabetes prevention or glycemic control; whether OA can plausibly complement evidence-based pharmacotherapy; and whether safety or regulatory constraints limit clinical translation.^{6,7,9–11,16–18,21,22,24,34–46}

Publications were excluded from detailed discussion if they focused on unrelated disease areas without a plausible metabolic link, lacked sufficient methodological detail, examined complex botanical mixtures without an identifiable OA contribution, or reported only chemical isolation without biological or translational relevance. Conference abstracts were used only to identify ongoing work and were not treated as definitive evidence.

2.3. Data extraction and synthesis

For each relevant source, information was extracted on study type, model or population, OA formulation, dose, route of administration, duration, comparator, co-intervention, metabolic endpoints, mechanistic endpoints, pharmacokinetic measures, safety findings, and main limitations. Human studies and trial records were additionally reviewed for sample size, eligibility criteria, intervention matrix, background therapy, primary and secondary endpoints, adverse-event monitoring, and patient relevance.^{9–11}

Findings were synthesized narratively according to a translational framework. Mechanistic studies were used to define biological plausibility, animal studies to evaluate *in vivo* metabolic effects and dose-translation issues, human pharmacokinetic studies to assess systemic exposure,

and clinical studies to evaluate prevention or adjunctive-treatment potential.^{4–11,16–18,21–23,34,35} Evidence was not pooled statistically because study designs, populations, formulations, doses, endpoints, and exposure durations were heterogeneous.

2.4. Areas of disagreement, evidence limitations, and bias considerations

Areas of disagreement were identified by comparing the direction, magnitude, and biological interpretation of findings across cell studies, animal models, human pharmacokinetic studies, clinical trials, and safety reports. Particular attention was paid to discrepancies between positive preclinical metabolic effects and cautionary or negative safety findings, especially hepatic toxicity and cholestatic signals observed under certain dose and duration conditions.^{16–18,21–23,37,38,44,47}

The main limitations of this narrative synthesis are the absence of formal systematic review screening procedures, lack of quantitative meta-analysis, potential publication bias favoring positive preclinical results, heterogeneity of OA formulations, and the limited number of completed human studies. The review also cannot exclude indexing bias, language bias, or selective citation bias. To reduce overinterpretation, conclusions were interpreted qualitatively according to whether support came mainly from *in vitro*, animal, pharmacokinetic, prevention-oriented clinical, or adjunctive-treatment evidence.^{4–11,14–18,21–23,34,35}

The central interpretive question was whether OA should be considered a plausible investigational adjunct in T2DM, particularly in patients receiving evidence-based pharmacotherapy. Evidence was therefore assessed in relation to glycemic endpoints, insulin resistance, lipid profile, inflammatory and oxidative stress biomarkers, hepatic and renal safety markers, adverse events, adherence, dietary acceptability, and the distinction between adjunctive benefit and unsupported replacement of established diabetes treatment.^{2,3,25–31,36–41,43–46,48}

3. Biological rationale for oleanolic acid in type 2 diabetes mellitus

The rationale for studying OA in T2DM is based on several intersecting mechanisms rather than on a single dominant target. T2DM develops through the combined effects of insulin resistance, β -cell dysfunction, excess hepatic glucose production, adipose tissue inflammation, ectopic lipid accumulation, oxidative stress, and vascular-metabolic injury.^{2,3} In this context, OA is better viewed as a pleiotropic metabolic modulator than as a selective glucose-lowering compound.^{49–51} This profile is attractive

for adjunctive therapy, but clinical relevance depends on whether pathway-level effects are reproducible, formulation-dependent, and large enough to influence patient-relevant endpoints.⁵²

3.1. Insulin signaling and glucose handling

Insulin resistance is central to T2DM and involves impaired insulin action in skeletal muscle, liver, adipose tissue, and other insulin-responsive organs, with downstream effects on glucose uptake, glycogen synthesis, lipid metabolism, and hepatic glucose production.^{52,53} Experimental evidence suggests that OA may interact with this pathway. A systematic review of insulin-resistant cell and animal models reported improved insulin sensitivity, increased glucose uptake, and reduced hepatic glucose production, probably through modulation of insulin receptor substrate/phosphatidylinositol 3-kinase/protein kinase B/forkhead box O1 signaling and related oxidative stress signalling.⁶

Oleanolic acid may also influence glucose and lipid handling through nuclear receptor and transporter-related mechanisms. *In vitro* and preclinical evidence indicates effects on peroxisome proliferator-activated receptor α /gamma signaling, metabolic nuclear receptor pathways, and glucose transporter 4 translocation.^{14,15} This supports the idea that OA may act at the interface of dysglycemia and dyslipidemia. However, whether these molecular effects occur at achievable human tissue concentrations remains uncertain and should be tested in formulation-specific pharmacodynamic studies.

3.2. Hepatic glucose production and lipid metabolism

The liver is a key target because fasting hyperglycemia in T2DM is strongly influenced by dysregulated hepatic glucose production. In diabetic and insulin-resistant models, OA has been reported to reduce fasting glucose, improve glucose and insulin tolerance, enhance hepatic insulin signaling, suppress gluconeogenesis, reduce hepatic lipid accumulation, and attenuate inflammatory mediators.^{16–18} These findings suggest that hepatic effects of OA may involve both glucose and lipid pathways. This is relevant to adjunctive therapy because metformin also acts partly by suppressing hepatic glucose production. In db/db mice, combined OA and metformin treatment produced greater improvements in blood glucose, insulin levels, liver pathology, insulin sensitivity, hepatic insulin signaling, and hepatic glucose production than either monotherapy alone.⁷ This provides a mechanistic bridge to the adjunctive-treatment hypothesis, but animal synergy should not be assumed to translate directly to humans

because dose, formulation, route, and exposure differ substantially from OA-enriched olive oil in clinical studies.

3.3. Oxidative stress, Nrf2 signaling, and mitochondrial function

Oxidative stress is closely linked to insulin resistance, β -cell dysfunction, endothelial injury, and diabetic complications.^{54,55} Chronic hyperglycemia, lipotoxicity, nutrient excess, and mitochondrial dysfunction increase reactive oxygen species production, which can impair insulin signaling and amplify inflammation. OA has repeatedly been studied as an antioxidant or redox-modulating compound, and recent reviews have summarized its natural sources, antioxidant mechanisms, therapeutic potential, and strategies for enhancing bioactivity.¹⁹ In hepatic insulin resistance models, OA improved mitochondrial parameters and reduced oxidative injury, with evidence implicating nuclear factor erythroid 2-related factor 2 (Nrf2) and glutathione-related antioxidant defences.¹⁶

The Nrf2 pathway is relevant because it regulates cytoprotective genes involved in antioxidant defense, detoxification, mitochondrial homeostasis, and cellular stress adaptation. Experimental reports suggest that OA may activate or stabilize Nrf2-related responses.^{4,16} However, Nrf2 activation should be treated as context-dependent rather than uniformly beneficial. Recent work also supports viewing OA as a modulator of an integrated organelle-stress network involving mitochondria, endoplasmic reticulum stress, autophagy, mitophagy, and apoptosis.²⁰ Human studies should therefore pair redox and organelle-stress biomarkers with clinical endpoints and safety monitoring, because stress-response modulation may vary by dose, tissue, disease stage, and duration of exposure.

3.4. Inflammation, adipose tissue dysfunction, and immunometabolism

Low-grade chronic inflammation contributes to insulin resistance and cardiometabolic complications.^{56,57} Adipose tissue expansion promotes macrophage infiltration, pro-inflammatory polarization, cytokine production, inflammasome activation, and release of mediators that interfere with insulin action. In high-fat diet-induced obese mice, OA improved insulin resistance, reduced adipocyte hypertrophy, decreased adipose tissue macrophage infiltration, and lowered the M1/M2 macrophage ratio. These effects were linked to reduced mitochondrial reactive oxygen species, mitogen-activated protein kinase signaling, and NLR family pyrin domain containing 3 inflammasome activation.²¹

Prediabetes models also support an immunometabolic role. In diet-induced prediabetic rats, OA improved lipid parameters and reduced platelet and immune-cell indices, pro-inflammatory cytokines, C-reactive protein, fibrinogen, and CD40 ligand.²² These findings are relevant because early dysglycemia is accompanied by inflammatory and prothrombotic changes. Still, these data remain preclinical, and it is not yet known whether OA-enriched formulations produce comparable immunometabolic effects in humans.

3.5. β -cell vulnerability and disease progression

Progression from insulin resistance to overt T2DM partly reflects failure of pancreatic β -cells to compensate for chronic metabolic stress.^{3,52,53} β -cells are especially vulnerable because insulin synthesis places a high secretory burden on the endoplasmic reticulum. Under physiological conditions, adaptive unfolded protein response signaling supports endoplasmic reticulum (ER) proteostasis, proinsulin folding, calcium handling, and β -cell survival. Under chronic glucotoxicity, lipotoxicity, inflammation, oxidative stress, or sustained insulin demand, this adaptive response may become maladaptive and contribute to β -cell dysfunction, apoptosis, impaired proinsulin processing, or loss of mature β -cell identity.^{20,54,55,58–60}

This distinction is important for interpreting the OA literature. General statements about “ β -cell protection” should not be taken to imply that OA has been shown to preserve β -cell mass or restore β -cell identity in humans. At present, the evidence is indirect. OA has been reported to influence β -cell-relevant pathways through oxidative stress reduction, inflammatory modulation, and improvement of systemic metabolic stress.^{4,5,19,20,23,49} However, direct evidence that OA modulates ER stress sensors, unfolded protein response branches, proinsulin folding, insulin granule maturation, or β -cell dedifferentiation in clinically relevant human settings remains limited.^{20,58–60}

Future studies should therefore evaluate β -cell biology more specifically. Relevant endpoints may include fasting and stimulated C-peptide, fasting insulin, proinsulin-to-insulin ratio, homeostatic model assessment of β -cell function (HOMA-B), oral glucose tolerance-derived insulin secretion indices, markers of ER stress and unfolded protein response activation, oxidative stress markers, and, where feasible, omics-based signatures of β -cell identity or dedifferentiation.^{26,29,58–60} Interpretation should also distinguish β -cell functional improvement from true disease modification, because improved glycemia can secondarily reduce glucotoxicity without proving direct β -cell preservation.

The strongest human signal compatible with disease-

modifying potential comes from PREDIABOLE, in which OA-enriched olive oil reduced progression from prediabetes to T2DM.¹⁰ This does not prove β -cell protection, but it suggests that OA-enriched functional foods may influence upstream metabolic processes. In established T2DM, the key question is different: whether OA can improve metabolic control or slow deterioration when β -cell dysfunction is already present, and pharmacologic therapy is in use.^{2,3,11}

3.6. Translational interpretation

Overall, the mechanistic case for OA is coherent but still largely preclinical. The most consistent themes are improved insulin signaling, reduced hepatic glucose output, modulation of oxidative and inflammatory stress pathways, and possible support of β -cell resilience. These pathways align with major components of T2DM pathophysiology and justify clinical testing, but they do not establish efficacy.

For these mechanisms to become clinically relevant, OA must achieve reproducible systemic exposure, show pharmacodynamic activity at achievable concentrations, remain compatible with standard drugs such as metformin, and demonstrate effects on clinically useful endpoints with appropriate safety monitoring. [Figure 2](#) summarizes the proposed network linking OA to insulin signaling, hepatic glucose production, oxidative stress, inflammation, and β -cell vulnerability.

4. Preclinical evidence for adjunctive use with metformin

The adjunctive-treatment hypothesis for OA is clinically relevant because most patients with established T2DM are treated within a pharmacologic framework rather than with isolated experimental compounds. Metformin remains an important comparator and partner because of its long-standing use, low cost, broad accessibility, low intrinsic risk of hypoglycemia, and central role in early pharmacologic management.^{2,3} An OA–metformin combination is therefore plausible if OA complements metformin's effects on hepatic glucose production, insulin sensitivity, lipid metabolism, oxidative stress, or inflammation without adding unacceptable safety or adherence burdens.

4.1. Mechanistic rationale for combining oleanolic acid with metformin

Metformin primarily improves hyperglycemia by reducing hepatic glucose production and improving insulin sensitivity through mechanisms involving mitochondrial function, cellular energy state, adenosine monophosphate-activated protein kinase signaling, gut-mediated pathways,

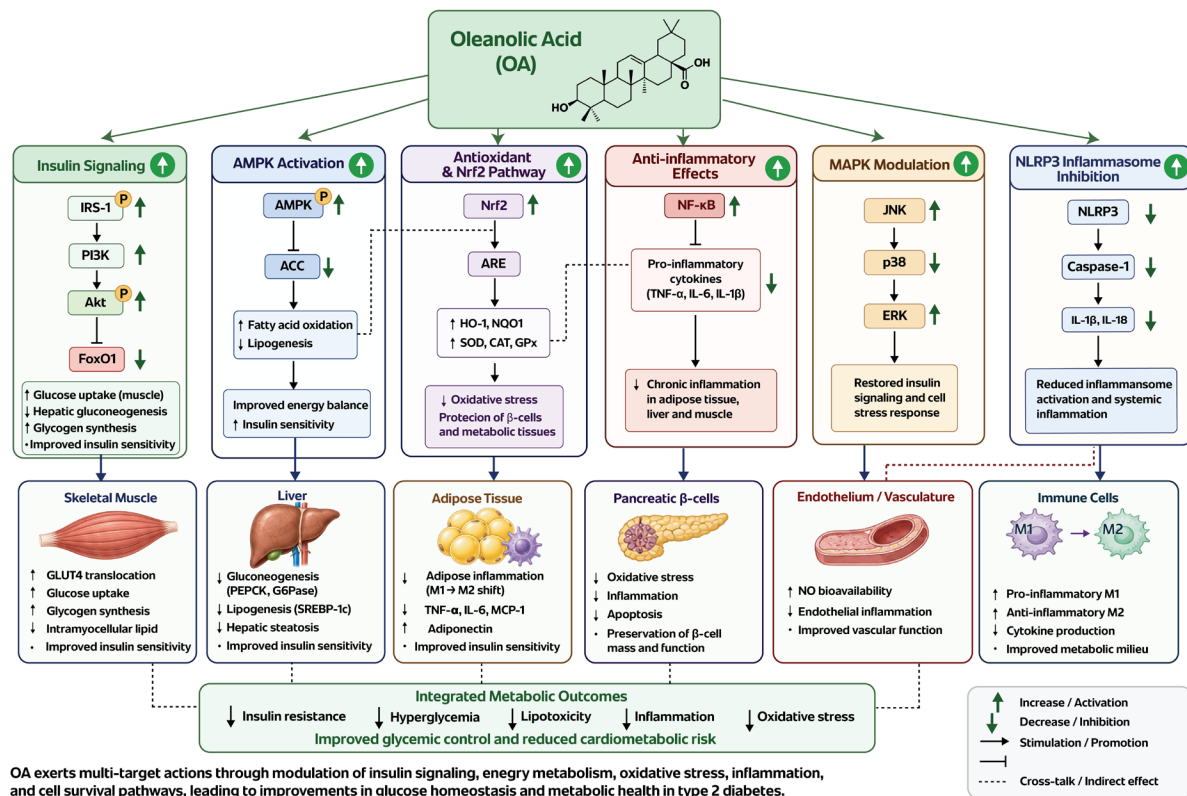


Figure 2. Mechanistic network linking OA to insulin resistance and glucose metabolism. OA may influence multiple interconnected pathways involved in type 2 diabetes pathophysiology, including insulin signaling, energy-sensing pathways, antioxidant responses, inflammatory signaling, mitochondrial stress, inflammasome activation, adipose tissue inflammation, endothelial function, and β-cell vulnerability.^{4-7,14-16,19-22,53-57} These pathway-level effects may converge on improved insulin sensitivity, reduced hepatic glucose production, lower oxidative and inflammatory stress, and improved cardiometabolic risk.^{6,7,16-18,21-23,25,28,29,47} However, their clinical relevance remains dependent on formulation-specific exposure and validation in human trials.^{9-13,61,62} Image created originally by the authors using Adobe Photoshop and Adobe Illustrator.

Abbreviations: ACC: Acetyl-CoA carboxylase; Akt: Protein kinase B; AMPK: Adenosine monophosphate-activated protein kinase; ARE: Antioxidant response element; CAT: Catalase; ERK: Extracellular signal-regulated kinase; FoxO1: Forkhead box O1; G6Pase: Glucose-6-phosphatase; GLUT4: Glucose transporter type 4; GPx: Glutathione peroxidase; HO-1: Heme oxygenase 1; IL: Interleukin; IRS-1: Insulin receptor substrate 1; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein 1; NF-κB: Nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; NO: Nitric oxide; NQO1: NAD(P)H quinone oxidoreductase 1; Nrf2: Nuclear factor erythroid 2-related factor 2; P: Phosphorylation; PEPCK: Phosphoenolpyruvate carboxykinase; PI3K: Phosphoinositide 3-kinase; SOD: Superoxide dismutase; SREBP-1c: Sterol regulatory element-binding protein 1c; TNF-α: Tumor necrosis factor-alpha.

and hepatic substrate handling.^{2,3,24} OA has been proposed to influence overlapping but not identical processes, including hepatic insulin signaling, glycogen metabolism, oxidative stress, inflammatory activation, and lipid accumulation.^{6,16} The rationale for combination therapy is therefore not duplication of effect, but convergence on hepatic and systemic metabolic dysfunction through partially distinct mechanisms.

This distinction matters clinically. OA would have limited value if it merely reproduced metformin's action at lower potency. Its potential lies in complementary effects

on oxidative-inflammatory stress, hepatic lipid handling, or insulin signaling, but this remains a hypothesis until supported by human pharmacodynamic and clinical endpoint data.

4.2. Evidence from db/db mouse models

The most direct preclinical evidence comes from a db/db diabetic mouse study comparing OA, metformin, combined OA and metformin treatment, and untreated diabetic controls. Mice received OA at 250 mg/kg, metformin at 100 mg/kg, or both for four weeks. Combination therapy produced greater improvement than monotherapy in

blood glucose, insulin levels, liver pathology, oral glucose tolerance, insulin sensitivity, hepatic insulin signaling, and hepatic glucose production.⁷

At the molecular level, the combined intervention increased markers of glycogen synthesis and decreased the expression or activity of markers linked to hepatic glucose output, including glycogen phosphorylase, peroxisome proliferator-activated receptor gamma coactivator 1 alpha, phosphoenolpyruvate carboxykinase, and glucose-6-phosphatase.⁷ These findings support the adjunctive hypothesis, but they do not prove clinical synergy. Strict pharmacologic synergy would require formal interaction testing across dose combinations; therefore, the evidence is best described as additive or potentially synergistic.

4.3. Dose translation and model limitations

The db/db model is useful but limited. It represents severe genetic obesity and leptin receptor deficiency, not the full heterogeneity of human T2DM. The four-week treatment period does not address durability, long-term safety, adherence, or interaction with contemporary therapies. The OA dose was also pharmacologic rather than dietary and differs substantially from the 30 mg OA dose used in human functional-oil studies.^{9,11}

This dose mismatch should be explicit in interpretation. A positive animal study supports biological plausibility, but it cannot be used to infer that 30 mg/day OA-enriched olive oil will produce the same effect in patients with T2DM.^{7,9} Conversely, a lipid matrix may improve absorption despite a lower nominal dose. Pharmacokinetic and pharmacodynamic studies are therefore needed to connect dose, formulation, exposure, and effect.

4.4. Quality and reproducibility considerations

The translational value of preclinical findings depends on design quality and reporting transparency. Animal studies intended to inform clinical translation should report randomization, blinding of outcome assessment, sample-size justification, sex, strain, diet composition, route of administration, formulation, batch characterization, prespecified endpoints, and adverse events. ARRIVE 2.0 provides a useful framework for improving animal-study reporting.⁶³

For OA-metformin translation, future preclinical work should incorporate dose-response designs, pharmacokinetic sampling, tissue exposure data, and formal interaction modeling. Diet-induced obesity models may complement genetic models by better reflecting lifestyle-associated insulin resistance. Endpoints should include not only glucose lowering but also hepatic safety

markers, renal markers, lipid profile, inflammatory biomarkers, and histology where appropriate.

4.5. Implications for OLTRAD and future trials

Preclinical evidence supports the plausibility of OA as an adjunct to metformin, but it does not establish clinical efficacy. The strongest animal evidence suggests that combined OA and metformin can improve glucose homeostasis, hepatic insulin signaling, and hepatic glucose production more than either treatment alone in db/db mice.⁷ Additional studies support effects on oxidative stress, inflammation, lipid metabolism, hepatic dysfunction, glucose homeostasis, renal-risk markers, and prediabetes-related immune activation.^{6,16–18,21–23,34,35}

OLTRAD is the appropriate next step because it evaluates OA-enriched functional olive oil in patients with established T2DM receiving metformin-based therapy¹¹. Its relevance will depend on whether the intervention improves glycated hemoglobin (HbA1c) or other clinically useful endpoints beyond standard care, whether the effect size is meaningful, and whether the intervention is safe, acceptable, and sustainable. The next step is therefore to determine in human trials whether measured exposure translates into outcomes that matter clinically.

4.6. Compatibility with SGLT2 inhibitors, GLP-1 receptor agonists, and dual incretin agonists

Although metformin is the most direct pharmacologic partner for the current OA adjunctive hypothesis, future OA trials will increasingly occur in a therapeutic landscape that includes SGLT2 inhibitors, GLP-1 receptor agonists, and dual incretin agonists.^{2,3} These agents are selected according to glycemic needs, cardiovascular risk, kidney disease, body-weight goals, hypoglycemia risk, cost, access, and patient preference.^{2,3,45} Therefore, OA should not be developed only in relation to metformin.

At present, there is no direct clinical evidence that OA improves, worsens, or interacts therapeutically with SGLT2 inhibitors, GLP-1 receptor agonists, or dual incretin agonists. Any proposed complementarity remains hypothetical. Potential points of interaction should be considered at pharmacodynamic, safety, and implementation levels. With SGLT2 inhibitors, future studies should monitor renal function, urinary albumin-to-creatinine ratio, volume status, edema or dehydration symptoms, and adverse events in patients also receiving renin-angiotensin system blockers, diuretics, or other drugs affecting renal hemodynamics.^{45,46} With GLP-1 receptor agonists and dual incretin agonists, gastrointestinal tolerability, appetite, dietary intake, weight loss, gallbladder-related events, and adherence may be

particularly relevant, especially because OA-enriched olive oil adds a fixed daily lipid load.^{2,3,10,11}

Potential pharmacokinetic interactions should also be documented. Metformin is less likely to be affected by CYP-mediated interactions because it is not substantially metabolized by cytochrome P450 enzymes and relies mainly on membrane transporters.³⁶ However, *in vitro* data indicate that OA can inhibit CYP1A2- and CYP3A4-mediated reactions and can be metabolized by CYP3A4 to hydroxylated products.^{40,41} The clinical relevance of these observations at concentrations achieved with OA-enriched olive oil remains uncertain.

Future OA trials should prespecify whether participants using SGLT2 inhibitors, GLP-1 receptor agonists, dual incretin agonists, insulin, or sulfonylureas are eligible, stratified, or excluded.^{2,3,11} Trial reports should describe background therapy, medication changes, rescue therapy, hypoglycemia, gastrointestinal adverse events, weight trajectories, renal markers, liver enzymes, dietary substitution, and adherence.^{25–31} This will be essential for determining whether OA-enriched formulations are compatible with contemporary standard care rather than only with metformin-based regimens.

5. Human bioavailability and formulation-dependent translation

Bioavailability is central to the interpretation of OA studies. Mechanistic and animal data are difficult to translate if oral administration does not produce reproducible systemic exposure at concentrations capable of influencing relevant tissues. This issue is especially important because OA is highly lipophilic, poorly water-soluble, and strongly dependent on formulation, postprandial lipid handling, and delivery-system design.^{9,12,13,61,62} Thus, the clinical question is not only whether OA has antidiabetic biology, but whether a feasible formulation can deliver OA safely and consistently during long-term diabetes care.

5.1. Horizontal comparison of delivery carriers

Oleanolic acid is widely distributed in plants and olive-derived products, but its hydrophobicity limits straightforward oral translation.^{4,5,12,13} Early analytical studies established that OA can be quantified in human serum or plasma, supporting the feasibility of human pharmacokinetic research.^{8,64} However, OA products should not be treated as interchangeable. The same nominal dose may produce different exposure when administered as purified OA, plant extract, capsule, suspension, lipid matrix, self-emulsifying system, cyclodextrin complex, phospholipid complex, liposome, polymeric nanoparticle, or albumin-based carrier.^{12,13,61,62,64–69} The main OA delivery

carriers and their translational implications are compared in Table 1.

The horizontal comparison (Table 1) highlights why positive findings with one OA formulation should not be generalized to another without pharmacokinetic bridging.^{12,13,61,62,64–69} Conversely, a negative trial using a poorly absorbed formulation would not necessarily disprove OA biology. For OA, clinical interpretation should remain tied to the exact formulation being tested.

5.2. Lipid matrices and functional olive oil

Lipid-based delivery is a rational strategy for OA because lipid vehicles can enhance solubilization, stimulate bile and pancreatic secretions, promote mixed micelle formation, influence enterocyte uptake, and potentially recruit intestinal lymphatic transport.^{12,13} These mechanisms support the use of an olive oil matrix rather than an isolated poorly soluble powder.

Oleanolic acid-enriched functional olive oil has additional translational advantages. Olive oil is familiar in Mediterranean dietary patterns, may be acceptable for long-term intake, and can serve as a food-based delivery matrix.^{70,71} Enrichment allows the OA dose to be standardized while preserving the lipid vehicle. This is clinically attractive, but it also complicates interpretation because olive oil itself may influence cardiometabolic outcomes.⁷¹ Matrix-matched control oils are therefore essential when the goal is to isolate the effect of OA enrichment.^{10,11}

BIO-OLTRAD provides the most directly relevant human pharmacokinetic evidence for OA-enriched functional olive oil. In this double-blind, randomized controlled study, participants received a single 30 mg OA dose in functional olive oil. OA reached measurable postprandial serum concentrations, with reported maximum concentrations of approximately 500–600 ng/mL and an AUC_{0–∞} of 2862.50 ± 174.50 ng·h/mL. The study also reported a physiological association of OA with serum albumin and triglyceride-rich lipoproteins, with lipoprotein-associated OA peaking after two to four h.⁹ BIO-OLTRAD should not be interpreted as evidence of antidiabetic efficacy, but it provides the pharmacokinetic bridge needed to justify longer clinical trials such as OLTRAD.^{9,11}

5.3. Clinically achievable concentrations versus *in vitro* exposure

The comparison between clinically achievable exposure and concentrations used in mechanistic studies remains a major translational gap. BIO-OLTRAD indicates that 30 mg OA delivered in functional olive oil can produce

Table 1. Horizontal comparison of oleanolic acid (OA) delivery carriers

Delivery carrier	Main rationale	Potential advantages	Main limitations	Translational interpretation	Key references
Conventional capsules or purified OA powder	Simple oral administration	Easy dosing; low manufacturing complexity	Poor dissolution; uncertain absorption; likely food effects	Should not be assumed bioequivalent to OA-enriched olive oil	12,64,65
Plant extracts or botanical mixtures	Natural-source delivery	May contain multiple bioactive compounds	OA contribution may be unclear; variable composition	Difficult to attribute effects specifically to OA	4,5
OA-enriched functional olive oil	Lipid-based food matrix	Supports solubilization and postprandial transport; acceptable dietary format; used in PREDIABOLE, BIO-OLTRAD, and OLTRAD	Adds dietary fat and energy; olive oil matrix may have independent effects; requires substitution monitoring	Currently the most clinically relevant OA formulation for type 2 diabetes mellitus translation	9–13,70,71
Self-emulsifying or self-nanoemulsifying systems	Enhance dispersion and intestinal absorption	May improve apparent bioavailability	More complex manufacturing; limited long-term human data	Promising formulation platform, but not interchangeable with food-based OA	62,66
Cyclodextrin or solid-dispersion systems	Improve solubility and permeability	May improve dissolution and cellular availability	Human exposure and chronic safety remain uncertain	Useful for formulation development, but clinical relevance requires exposure-response data	65,67
Liposomes, polymeric nanoparticles, albumin carriers, and other nanocarriers	Controlled release or tissue distribution	Potentially improved stability, exposure, or targeting	Regulatory complexity, cost, scalability, and safety challenges	Should be viewed as a distinct drug-development pathway rather than a dietary adjunct	68,69

measurable systemic exposure in humans.⁹ However, many cell-culture and mechanistic studies evaluate OA under simplified exposure conditions that do not reproduce intestinal absorption, first-pass handling, albumin binding, lipoprotein transport, tissue distribution, or chronic dietary use.^{4,6,12–15,61,62} Therefore, *in vitro* pathway modulation cannot be assumed to occur in humans after a 30 mg OA dose.

Future pharmacodynamic studies should directly connect measured serum OA, lipoprotein-associated OA, and, where possible, tissue-relevant biomarkers with downstream metabolic effects.^{9,12,13} Relevant endpoints include postprandial glucose, insulin, triglyceride-rich lipoprotein fractions, inflammatory mediators, oxidative stress markers, hepatic glucose-output surrogates, and β -cell stress markers.^{7,9,16,21,22,26,29} Without exposure-sensitive biomarkers, a negative clinical trial could reflect inadequate delivery rather than absence of biological activity.

5.4. Dose, timing, and pharmacodynamic implications

Human bioavailability data have practical implications for trial design. Dose should be interpreted in relation to formulation, not only milligrams of OA. A 30 mg dose

in functional olive oil cannot be assumed equivalent to 30 mg in a capsule, extract, suspension, or nanoparticle system.^{9,12,13,68,69} Timing with meals may also matter because lipid digestion and postprandial lipoprotein formation are likely to affect systemic transport.^{9,12,13}

Longer trials should focus on HbA1c, fasting glucose, continuous glucose monitoring metrics, insulin resistance indices, body weight, lipid profile, liver enzymes, kidney markers, adverse events, and adherence.^{2,3,26,29–31} Because the assigned oil dose in PREDIABOLE and OLTRAD is 55 mL/day, trials should also assess whether participants replace other culinary fats or simply add the study oil to their usual diet.^{10,11}

5.5. Low-dose oil formulations and composite carrier strategies

The 30 mg/day OA dose delivered through functional olive oil is attractive because it is relatively low compared with pharmacologic doses used in many animal studies and has been tested in a familiar dietary matrix.^{7,9–11} However, the current 55 mL/day oil volume may limit implementation outside Mediterranean-style dietary patterns.^{9–11,70} Future research should therefore evaluate whether lower oil volumes, improved enrichment, or composite carrier strategies can preserve systemic exposure while reducing dietary burden.

Composite strategies could include lipid matrices combined with phospholipid complexes, cyclodextrin inclusion, solid dispersion, self-emulsifying systems, self-microemulsifying systems, liposomes, polymeric nanoparticles, or albumin-based carriers.^{61,62,65–69}

Such approaches may be useful if they reduce oil volume, improve exposure reproducibility, or allow better dose standardization. However, each composite carrier should be treated as a distinct formulation requiring its own pharmacokinetic, safety, manufacturing, and regulatory evaluation.^{12,13,61,62,64–69} Improved solubility *in vitro* should not be equated with clinical readiness.

6. Clinical evidence: from prediabetes prevention to adjunctive therapy

Clinical evidence for OA in diabetes remains limited, but it follows a relatively clear translational sequence. The available human data do not yet establish OA as a treatment for established T2DM, but they do provide three clinically relevant building blocks: a prevention trial in individuals with prediabetes, a human bioavailability trial using OA-enriched functional olive oil, and an ongoing adjunctive-therapy trial in patients with T2DM receiving metformin-based treatment.^{9–11} This sequence is important because it follows a recognizable translational pathway: first, identify a plausible biological effect; second, demonstrate systemic exposure in humans; third, test whether the intervention improves clinically meaningful endpoints in the intended patient population. Table 2 summarizes the current translational evidence base and highlights the main limitations and bias sources that should guide interpretation.

6.1. PREDIABOLE and the prevention signal

PREDIABOLE is the most important published intervention trial of OA-enriched olive oil in glucose-metabolism disorders. In this multicenter, randomized, double-blind, controlled trial, adults with prediabetes received either 55 mL/day of OA-enriched olive oil, providing approximately 30 mg OA/day, or the same olive oil without OA enrichment.¹⁰ The matrix-controlled design is important because olive oil itself may influence cardiometabolic outcomes.⁷¹

The main clinical signal was reduced progression from prediabetes to T2DM. The trial reported 48 new diabetes cases: 31 in the control group and 17 in the OA-enriched group. The multivariable-adjusted hazard ratio for incident T2DM was 0.45, with a 95% confidence interval of 0.24–0.83, and intervention-related adverse effects were not reported.¹⁰ These findings support prevention-oriented

potential and long-term functional-food feasibility.

However, PREDIABOLE should not be interpreted as proof of treatment efficacy in established T2DM. Participants were not selected for inadequate glycemic control on metformin, and the endpoint was diabetes onset rather than HbA1c reduction in diagnosed T2DM. Its main value for this review is therefore proof of concept: OA-enriched olive oil can be administered long-term, compared with a matched oil control, and is associated with clinically meaningful metabolic outcomes.¹⁰

6.2. BIO-OLTRAD and OLTRAD: from exposure to adjunctive testing

BIO-OLTRAD provides the pharmacokinetic bridge between prevention-oriented findings and adjunctive-treatment trials. In this double-blind, randomized, controlled human study, 22 healthy participants received a single 30 mg OA dose formulated as functional olive oil. OA reached measurable postprandial serum concentrations, with maximum concentrations around 500–600 ng/mL and an AUC_{0–∞} of 2862.50 ± 174.50 ng·h/mL. OA was also associated with serum albumin and triglyceride-rich lipoproteins, supporting the biological plausibility of lipid-matrix delivery.⁹

These data do not establish antidiabetic efficacy, but they show that the tested formulation produces systemic exposure. This matters because a prevention or treatment signal is more credible when the intervention is known to reach circulation. BIO-OLTRAD also supports treating OA-enriched olive oil as a specific formulation rather than as generic OA.⁹

OLTRAD is the key ongoing test of the adjunctive hypothesis. It is designed as a prospective, parallel-group, randomized, double-blind, controlled trial in patients with established T2DM receiving metformin therapy, either alone or with other antidiabetic drugs. Participants receive 55 mL/day of OA-enriched or control olive oil for 12 months, with HbA1c as the main glycemic variable.¹¹ This design directly addresses whether OA-enriched functional olive oil adds metabolic benefit beyond metformin-based standard care.

6.3. Clinical interpretation and evidence gaps

The clinical interpretation of OA will depend on effect size, safety, adherence, and formulation specificity. A modest HbA1c reduction may be meaningful if the intervention is safe, inexpensive, acceptable, weight-neutral or weight-favorable, and compatible with current therapy.^{2,3} Conversely, a statistically significant but very small effect would not justify adoption if adherence is poor, caloric intake increases, or adverse effects emerge.

Table 2. Translational evidence map for OA in T2DM

Evidence level	Main evidence type	Key findings	Translational value	Main limitations	Main sources of bias	Key references
Mechanistic plausibility	Cell and pathway-focused studies	OA may modulate insulin signaling, oxidative stress, inflammation, lipid metabolism, and glucose handling	Defines biological rationale and candidate biomarkers	Achievable human tissue concentrations remain uncertain	<i>In vitro</i> concentration bias; simplified cell systems; short exposure; lack of protein binding or lipoprotein transport	4–6,14,15
β-cell stress biology	Mechanistic evidence on ER stress, UPR, proinsulin handling, and dedifferentiation	β-cell failure involves ER stress, maladaptive UPR, proinsulin misfolding, oxidative stress, and possible loss of β-cell identity	Strengthens biological rationale for β-cell-related endpoints	Direct OA effects on these pathways in humans are not established	Mechanistic extrapolation; indirect evidence; limited OA-specific β-cell data	7,16,21,22,47,58–60
<i>In vivo</i> metabolic effects	Rodent models of diabetes, obesity, insulin resistance, and prediabetes	OA improved glucose tolerance, insulin sensitivity, hepatic metabolic markers, inflammation, and lipid parameters in selected models	Supports <i>in vivo</i> plausibility and endpoint selection	Species differences, high doses, short exposure, variable formulations	Animal-model bias; high-dose bias; short-duration bias; publication bias; limited sex/strain generalizability	7,16–18,21–23,47
Adjunctive preclinical therapy	OA plus metformin in db/db mice	Combined treatment improved glycemic and hepatic outcomes more than monotherapy in one model	Supports adjunct-to-metformin hypothesis	Does not prove human synergy; dose and exposure differ from functional olive oil	Single-model bias; high-dose bias; short-duration bias; no formal interaction modeling	7,9,11
Human bioavailability	BIO-OLTRAD	A 30 mg OA dose in functional olive oil produced measurable serum exposure and albumin/lipoprotein-associated transport	Demonstrates formulation-dependent human systemic exposure	Healthy volunteers; acute dosing; no efficacy endpoints	Healthy-volunteer bias; acute-exposure bias; no exposure-response threshold	9,10
Prevention-oriented clinical trial	PREDIABOLE	OA-enriched olive oil reduced progression from prediabetes to T2DM compared with control olive oil	Proof of concept in a clinically relevant risk population	Prevention trial, not established T2DM treatment	Endpoint-context bias; limited generalizability to treated T2DM; dietary adherence and matrix effects	10,11
Adjunctive clinical trial	OLTRAD trial registry	OA-enriched olive oil is being tested as an adjunct to metformin-based therapy in established T2DM	Directly tests the main clinical hypothesis	Results not yet available; formulation-specific conclusions	Anticipation bias; no efficacy results yet; background-therapy heterogeneity	11,36–41,43–45,48
Safety and regulation	Preclinical toxicology, interaction studies, and regulatory guidance	Hepatic safety, drug interactions, health claims, and formulation classification require monitoring	Defines risk-management and communication needs	Long-term human safety in complex T2DM populations remains limited	Safety-reporting bias; dose-extrapolation bias; regulatory-region heterogeneity	36,48,72–76

Abbreviations: ER: Endoplasmic reticulum; OA: Oleanolic acid; T2DM: Type 2 diabetes mellitus; UPR: Unfolded protein response.

Because the intervention is delivered as olive oil, glycemic outcomes should be interpreted together with body weight, waist circumference, lipid profile, blood pressure, liver enzymes, kidney markers, inflammatory biomarkers, adverse events, medication changes, and dietary substitution. Intake of 55 mL/day of oil contributes substantial dietary fat and energy; therefore, trials should assess whether participants replace other culinary fats or simply add the study oil to their usual diet.^{10,11}

Several gaps remain. No completed large trial has shown that OA lowers HbA1c in patients with established T2DM receiving standard therapy. Human evidence is concentrated on OA-enriched olive oil, which prevents direct extrapolation to capsules, extracts, or nanoformulations. Exposure-response relationships remain undefined, and long-term safety data are sparse in patients with polypharmacy, liver disease, kidney disease, or cardiovascular disease.

At present, OA-enriched functional olive oil should be viewed as an investigational adjunct. PREDIABOLE provides prevention-oriented proof of concept, BIO-OLTRAD confirms formulation-dependent systemic exposure, and OLTRAD is positioned to test adjunctive benefit in metformin-treated T2DM.^{9–11} Together, these studies provide a coherent development pathway, but not yet enough evidence for clinical recommendation.

7. Safety, interactions, and regulatory considerations

Any adjunctive intervention for T2DM would likely be used chronically and in patients with comorbidities, polypharmacy, and variable dietary adherence; safety is therefore a central issue for OA development. A food-derived compound should not be assumed to be safe once it is enriched, concentrated, reformulated, or consumed at a standardized daily dose. For OA, this issue is particularly important because experimental studies describe both hepatometabolic benefits and dose- or duration-dependent hepatic toxicity signals.^{37,38,44}

7.1. Exposure scenario and hepatic safety

A key distinction is the difference between habitual dietary exposure and controlled exposure to OA-enriched formulations. Conventional olive products contain variable amounts of OA depending on cultivar, processing, fraction, storage, and analytical method.⁵ In contrast, PREDIABOLE and OLTRAD use a standardized intervention of 55 mL/day olive oil providing approximately 30 mg/day OA.^{9–11} This improves trial control but creates a different exposure scenario from ordinary dietary intake.

The liver is both a potential target of OA benefit and

a potential organ of toxicity. OA has been reported to improve hepatic insulin resistance, lipid accumulation, oxidative stress, inflammation, and metabolic signaling in experimental diabetes models.^{16,47} However, repeated oral OA administration in mice produced cholestatic liver injury at higher doses, and longer exposure to lower doses has been associated with liver injury, fibrosis, altered bile acid-metabolism genes, and transforming growth factor beta/Smad activation.^{37,44} Additional work supports the view that OA may be hepatoprotective in some contexts but hepatotoxic at higher doses or prolonged exposure.³⁸

These animal toxicology findings are not directly comparable to 30 mg/day OA-enriched olive oil in humans, but they identify a plausible safety domain. Future trials should therefore monitor alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, and prespecified hepatic adverse-event thresholds. This is especially relevant in T2DM because metabolic dysfunction-associated steatotic liver disease, gallbladder disease, alcohol exposure, and concomitant hepatotoxic medications may modify risk.

7.2. Renal, cardiovascular, and drug-interaction considerations

Renal safety is also important because chronic kidney disease is a common diabetes complication requiring systematic screening and longitudinal monitoring⁴⁵, and preclinical studies of OA have reported effects on diabetic nephropathy and renal inflammatory or injury markers.^{34,35,46} The clinical history of bardoxolone methyl, a synthetic triterpenoid Nrf2 activator, is a useful cautionary example: despite early improvement in estimated glomerular filtration rate, the BEACON trial in patients with T2DM and advanced chronic kidney disease was terminated because of excess heart failure events.³⁹ Bardoxolone methyl is not OA, but this experience shows that triterpenoid-related mechanisms can produce unexpected safety signals in high-risk diabetic populations.

For OA-enriched olive oil, renal monitoring should include serum creatinine, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and adverse events related to edema or volume status, especially if future trials include patients with chronic kidney disease or combine OA with SGLT2 inhibitors, renin-angiotensin system blockers, diuretics, or other drugs affecting renal hemodynamics.

Potential drug interactions should be considered at pharmacokinetic and pharmacodynamic levels. *In vitro* data show that OA can inhibit CYP1A2- and CYP3A4-mediated reactions and can be metabolized by CYP3A4 to

hydroxylated products.^{40,41} The clinical relevance of these findings at concentrations achieved with OA-enriched olive oil is uncertain. Metformin is less likely to be affected by CYP-mediated interactions because it is not substantially metabolized by cytochrome P450 enzymes and relies mainly on membrane transporters for pharmacokinetics and response.³⁶ Nevertheless, trials should document concomitant medications, hypoglycemia events, dose changes, and adverse events, particularly in participants using insulin, sulfonylureas, glinides, anticoagulants, antiplatelet agents, statins, or antihypertensive drugs.

7.3. Dietary safety, adherence, and implementation risk

The olive oil matrix introduces safety and feasibility issues that are absent from purified-compound trials. A daily dose of 55 mL oil contributes substantial fat and energy.^{10,11} If it replaces other culinary fats, it may fit a Mediterranean-style diet; if it is added without compensation, it could increase total energy intake and affect body weight, lipid profile, and glycemic control. Trials should therefore record dietary substitution, total energy intake, body weight, waist circumference, gastrointestinal symptoms, taste acceptability, and adherence.

Adherence should not be treated as a minor operational detail. For a chronic functional-food adjunct, feasibility depends on taste, cost, culinary habits, gastrointestinal tolerability, cultural dietary fit, and willingness to consume a fixed daily volume of oil. Returned oil volume, bottle weight, dietary records, structured interviews, and exposure markers such as serum or lipoprotein-associated OA should be used where possible.

7.4. Regulatory positioning and disease-claim restrictions

The regulatory status of OA-enriched products depends on jurisdiction, formulation, concentration, intended use, and claims. A product positioned as a conventional food, functional edible oil, dietary supplement, botanical product, natural health product, complementary medicine, medical food, or drug-like formulation may face different evidentiary, manufacturing, labeling, quality-control, and post-market surveillance requirements.^{42,43,48,72–76}

In the United States, conventional foods and dietary supplements may carry certain nutrition, health, or structure/function claims, but claims to diagnose, mitigate, treat, cure, or prevent diabetes may cause a product to be regulated as a drug unless the claim is specifically authorized.^{48,72} In the European Union, nutrition and health claims are governed by an authorization framework, and disease-risk reduction claims require

scientific assessment and inclusion in the permitted claims system.^{43,73} In Canada, natural health products are regulated under a dedicated framework and require evidence supporting safety, efficacy, and quality for licensed claims.⁷⁴ In Australia, listed complementary medicines require sponsors to hold evidence supporting indications and claims.⁷⁵ In Japan, Foods with Function Claims are based on notifier responsibility and scientific evidence, but the claim framework should not be confused with authorization to treat established disease.⁷⁶

These distinctions matter in T2DM because patient-facing claims can easily shift from “supports metabolic health” to implied treatment or prevention of diabetes. At present, OA-enriched functional oil should be described as an investigational adjunct or research formulation, not as a proven antidiabetic therapy.^{9–11,48} Patient-facing communication should clearly state that OA-enriched functional foods may complement, but should not replace, evidence-based pharmacotherapy.^{2,3,48}

8. Patient-centered outcomes and clinical trial endpoints

Endpoint selection in OA trials should reflect both the proposed mechanism of action and the practical realities of a food-based adjunctive intervention. [Table 3](#) proposes a practical endpoint framework for future OA trials in T2DM.

Because OA-enriched olive oil is both a dietary intervention and a bioactive formulation, trial outcomes should not be limited to HbA1c. HbA1c remains the most appropriate primary endpoint for longer adjunctive-treatment trials because it reflects average glycemia over approximately two to three months and is embedded in diabetes guidelines and clinical decision-making.^{2,3,26} However, HbA1c should be interpreted alongside fasting plasma glucose, postprandial glucose, insulin resistance indices, body weight, lipid profile, cardiometabolic markers, hepatic and renal safety markers, adherence, and patient-reported outcomes.^{25,27,28,51}

Continuous glucose monitoring may be particularly informative in OA trials because the intervention is consumed with meals and may influence postprandial glucose and lipid handling. A prespecified continuous glucose monitoring (CGM) substudy could assess time in range, time above range, time below range, mean glucose, glycemic variability, and postprandial excursions after meals containing the study oil. These metrics may detect changes in glycemic quality that are not captured by HbA1c alone and may also identify hypoglycemia risk in patients receiving insulin or insulin secretagogues.²⁹

Table 3. Proposed clinical, safety, exposure, and patient-centered endpoints for future OA trials in type 2 diabetes mellitus

Endpoint domain	Assessment indices/core endpoints	Reference criteria or interpretive notes	Purpose	Suggested priority	Key references
Glycemic efficacy	HbA1c; fasting plasma glucose, postprandial glucose	Use standardized laboratory methods; prespecify timing, baseline adjustment, rescue-therapy rules, and clinically meaningful effect size	Determine clinical metabolic benefit	Primary or key secondary	2,3,26
Glucose dynamics	Time in range, time above range, time below range, mean glucose, glycemic variability, postprandial excursions	Use consensus CGM definitions, including time in range 70–180 mg/dL, time below range <70 mg/dL, and time above range >180 mg/dL	Capture effects missed by HbA1c and identify hypoglycemia risk	CGM substudy or secondary	29
Insulin resistance and β -cell function	Fasting insulin, C-peptide, HOMA-IR, HOMA-B, oral glucose tolerance-derived indices, proinsulin-to-insulin ratio	Treat HOMA indices as surrogate measures; interpret C-peptide and proinsulin indices in relation to background therapy and disease duration	Clarify mechanism and responder phenotype	Secondary or mechanistic	2,3,26,58–60
Cardiometabolic risk	Body weight, waist circumference, blood pressure, lipid profile, apolipoprotein B where feasible	Interpret together with dietary substitution, total energy intake, and background lipid-lowering therapy	Assess broader metabolic benefit or harm	Secondary	2,3,25,27,28
Inflammation and oxidative stress	High-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor α , oxidative stress markers, Nrf2-related markers	Exploratory unless powered; avoid treating biomarker change as clinical efficacy	Test mechanistic hypotheses	Exploratory	6,16,19,21,22
Hepatic and renal safety	Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, serum creatinine, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio	Prespecify hepatic and renal stopping or monitoring thresholds; interpret in relation to baseline MASLD, CKD, gallbladder disease, and concomitant drugs	Detect hepatocellular, cholestatic, and renal safety signals	Core safety	37–39,44–46
Drug interaction and medication burden	Hypoglycemia events, rescue therapy, medication dose changes, concomitant SGLT2 inhibitors, GLP-1 receptor agonists, dual incretin agonists, insulin, sulfonylureas, statins, antihypertensives, anticoagulants	Report background therapy at baseline and throughout follow-up; prespecify subgroup or stratified analyses where feasible	Interpret adjunctive effect and safety	Core safety/clinical	2,3,36,40,41,45
Exposure and adherence	Serum OA, lipoprotein-associated OA, bottle counts, returned oil volume, dietary records, meal timing, replacement of other culinary fats	No accepted therapeutic OA threshold exists; exposure should be linked to pharmacodynamic and clinical endpoints	Link formulation exposure to response and adherence	Pharmacokinetic subset/core adherence	9–13
Patient-reported and implementation outcomes	Gastrointestinal tolerability, taste acceptability, treatment burden, dietary satisfaction, quality of life, willingness to continue, cost, cultural dietary fit	Use prespecified patient-reported outcome instruments where feasible; report missing data and discontinuation reasons	Evaluate feasibility and patient relevance	Secondary or implementation	30,31,77

Abbreviations: CGM: Continuous glucose monitoring; CKD: Chronic kidney disease; GLP-1: Glucagon-like peptide 1; HbA1c: Glycated hemoglobin; HOMA-B: Homeostatic model assessment of β -cell function; HOMA-IR: Homeostatic model assessment of insulin resistance; MASLD: Metabolic dysfunction-associated steatotic liver disease; Nrf2: Nuclear factor erythroid 2-related factor 2; OA: Oleanolic acid; SGLT2: Sodium-glucose cotransporter 2.

Mechanistic endpoints should be selected to match the proposed biology of OA. Fasting insulin, C-peptide, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), oral glucose tolerance-derived indices, triglycerides, liver enzymes, high-sensitivity C-reactive protein, interleukin-6, oxidative stress markers, and lipoprotein-associated OA may help clarify whether any clinical effect is linked to insulin sensitivity, hepatic metabolism, inflammation, oxidative stress, or formulation-dependent exposure.^{6,7,9,16,21,22} These biomarkers should remain supportive rather than substituting for clinical endpoints.

Safety endpoints are essential because OA has shown both hepatometabolic benefit and hepatic toxicity signals in experimental settings. Core monitoring should include alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, serum creatinine, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, hypoglycemia events, gastrointestinal symptoms, body weight, blood pressure, edema, adverse events, serious adverse events, and medication changes.^{37–39,44–46} Hepatic, renal, and cardiovascular monitoring should be proportionate to baseline risk and background therapy.

Adherence and dietary substitution should be treated as clinical outcomes, not only as trial logistics. In PREDIABOLE and OLTRAD, the assigned oil dose was 55 mL/day.^{10,11} This amount may be feasible in Mediterranean-style dietary patterns, but it can increase total energy intake if it is added rather than substituted for other fats. Trials should therefore assess returned oil volume, bottle weight, dietary records, total energy intake, replacement of other culinary fats, taste acceptability, gastrointestinal tolerability, cost, and willingness to continue.

Patient-reported outcomes are also important because the real-world value of a functional-food adjunct depends on daily use. Relevant domains include treatment burden, dietary satisfaction, gastrointestinal comfort, perceived ease of use, diabetes-related distress, quality of life, and compatibility with usual meals. These outcomes should be prespecified and reported according to established guidance for patient-reported outcomes in randomized trials.^{30,31}

Overall, the endpoint framework for OA trials should match its hypothesized role: adjunctive metabolic support rather than replacement pharmacotherapy. A favorable study would need to show not only improved HbA1c or glycemic variability, but also acceptable safety, stable or favorable weight and lipid effects, good adherence, and patient acceptability. Conversely, biomarker improvement

without patient-relevant benefit would not be enough to support clinical use.

9. Translational gaps and future research agenda

The evidence base for OA in T2DM has moved beyond isolated mechanistic observations, but it remains insufficient for clinical recommendation. Current support comes from four connected domains: preclinical studies showing biological plausibility, human pharmacokinetic data demonstrating formulation-dependent exposure, PREDIABOLE suggesting prevention-oriented benefit in prediabetes, and OLTRAD testing the adjunctive-treatment hypothesis in metformin-treated T2DM.^{6,9–11} The next stage should clarify which patients may benefit, which formulation is clinically relevant, whether exposure predicts response, and whether long-term use is safe.

9.1. Target population and responder phenotype

The first unresolved question is the intended clinical niche. OA could be evaluated in at least three different groups: individuals with prediabetes, patients with early T2DM and preserved β -cell function, and patients with established T2DM characterized by insulin resistance, hepatic steatosis, hypertriglyceridemia, or low-grade inflammation. These populations should not be merged without stratification. Prevention trials should focus on incident diabetes and cardiometabolic-risk modification, whereas adjunctive-treatment trials should prioritize HbA1c, CGM-derived metrics, safety, adherence, and medication burden. PREDIABOLE supports the prevention hypothesis, while OLTRAD addresses the established-T2DM adjunctive hypothesis.^{10,11} Future studies should therefore prespecify whether OA is being tested as a prevention strategy, a dietary adjunct, a formulation platform, or a pharmaceutical lead. Phenotype-guided designs may be particularly useful. Patients with higher insulin resistance, elevated triglycerides, metabolic dysfunction-associated steatotic liver disease, inflammatory activation, early renal-risk markers, or early disease duration may be more likely to show a measurable response, although this remains unproven.^{18,23,34,50,51}

9.2. Exposure-response and formulation standardization

A major translational gap is the lack of exposure-response data. BIO-OLTRAD showed that 30 mg OA in functional olive oil produces measurable serum concentrations and transport through albumin and triglyceride-rich lipoproteins.⁹ However, it is unknown whether higher OA exposure predicts greater glycemic improvement,

stronger biomarker changes, more adverse events, or no clinically relevant difference. Future trials should include pharmacokinetic or sparse-sampling substudies to link adherence, absorption, systemic exposure, and clinical response.

Formulation standardization is equally important. The current human evidence mainly concerns OA-enriched olive oil, not generic OA. A 30 mg OA dose delivered in olive oil cannot be assumed to be equivalent to the same nominal dose in a capsule, extract, suspension, or nanoformulation.^{9,68} Trial reports should specify OA source, purity, enrichment method, oil volume, fatty acid profile where relevant, coexisting triterpenes or phenolics, storage conditions, batch consistency, and analytical confirmation of dose. Comparator selection should also match the scientific question: testing OA enrichment requires a matrix-matched control oil, whereas capsule-based formulations require a different comparator strategy.⁷¹

9.3. Trial design, biomarkers, and reporting quality

Future OA trials should follow standards expected for pharmacologic adjuncts, even when the intervention is positioned as a functional food or nutraceutical. Protocols should prespecify the primary endpoint, statistical analysis plan, rescue medication rules, adherence criteria, safety thresholds, missing-data handling, subgroup analyses, and exposure-response analyses. TIDieR, SPIRIT, and CONSORT provide useful frameworks for intervention description, protocol design, and trial reporting.^{77–79}

Mechanistic biomarkers should be included, but they should not replace clinical endpoints. Preclinical evidence implicates insulin signaling, hepatic glucose production, oxidative stress, Nrf2-related defenses, inflammatory signaling, macrophage activation, and lipid metabolism.^{6,16,21,22,47} Human studies should therefore select biomarkers that directly map to the hypothesized mechanism, such as fasting insulin, C-peptide, HOMA-IR, triglycerides, liver enzymes, high-sensitivity C-reactive protein, interleukin-6, oxidative stress markers, and lipoprotein-associated OA. Broad exploratory biomarker panels without prespecified interpretation should be avoided.

9.4. Methodological limitations, safety uncertainty, and implementation bias

The interpretation of OA evidence is limited by several methodological and translational biases. Mechanistic studies often use simplified cell systems, high OA concentrations, short exposures, and endpoints that may not correspond to achievable human tissue

concentrations.^{4,6,14–16} Animal studies frequently use high pharmacologic doses, short treatment periods, and models such as db/db mice that capture selected features of diabetes but not the full heterogeneity of human T2DM.^{7,16–18,21–23,47} The db/db combination study is useful for biological plausibility, but its 250 mg/kg OA dose, four-week duration, and genetic-obesity model should not be extrapolated directly to 30 mg/day OA-enriched olive oil in humans.^{7,9,11}

Human evidence is concentrated in a small number of studies using OA-enriched olive oil. PREDIABOLE supports prevention-oriented potential in prediabetes, BIO-OLTRAD supports formulation-dependent systemic exposure, and OLTRAD is testing adjunctive use in metformin-treated T2DM.^{9–11} However, no completed large clinical trial has yet established that OA lowers HbA1c or improves patient-relevant outcomes in established T2DM beyond standard care.^{2,3,9–11,26} This prevents broad extrapolation to capsules, extracts, botanical mixtures, or nanoformulations.^{12,13,61,62,64–68,68}

The evidence base also contains positive metabolic findings and cautionary safety findings. OA has shown hepatometabolic benefits in several experimental models,^{16–18,66} but published toxicology studies indicate that OA can produce hepatotoxic or cholestatic effects under certain dose and exposure conditions.^{37,38,44} These findings are not directly comparable to 30 mg/day OA-enriched olive oil in humans, but they justify careful hepatic, renal, cardiovascular, gastrointestinal, and hypoglycemia monitoring in future trials.^{25,27,28,37–39,44–46}

Implementation should be studied alongside efficacy. A daily dose of 55 mL olive oil may be feasible in Mediterranean-style dietary patterns but difficult in other settings.^{10,11,70,71} Trials should assess dietary substitution, total energy intake, adherence, taste acceptability, gastrointestinal tolerability, cost, and willingness to continue.^{30,31} If OA-enriched products are expensive or marketed with exaggerated claims, they could widen disparities or divert patients from evidence-based therapy. Patient-facing communication should therefore clearly distinguish adjunctive use from medication replacement.^{2,3,48}

9.5. Proposed research agenda

A staged development pathway is most appropriate. First, mechanistic human studies should link OA exposure to insulin sensitivity, postprandial glucose and lipid metabolism, oxidative-inflammatory biomarkers, β -cell stress markers, and hepatic safety markers.^{2,3,16,21,22,37,38,44} These studies should compare clinically achievable OA exposure with concentrations used in *in vitro* and animal studies.^{4,6,9,12–16,61,62}

Second, randomized controlled trials in metformin-treated T2DM should test HbA1c and continuous glucose monitoring outcomes using matrix-matched comparators, standardized dietary-substitution instructions, and prespecified safety thresholds.^{2,3,10,11,26,29} These trials should report whether background SGLT2 inhibitors, GLP-1 receptor agonists, dual incretin agonists, insulin, or sulfonylureas were allowed, stratified, or excluded.^{2,3,45}

Third, larger multicenter studies should evaluate durability, safety, responder phenotypes, exposure-response relationships, and compatibility with contemporary standard care.^{2,3,9,25,27–31,45} Particular attention should be paid to patients with metabolic dysfunction-associated steatotic liver disease, chronic kidney disease, cardiovascular disease, gallbladder disease, polypharmacy, and high gastrointestinal symptom burden.^{18,25,27,28,45,46}

Fourth, pragmatic studies should assess adherence, cost, dietary fit, generalizability, health-literacy demands, and the risk that OA-enriched products may be misunderstood as replacements for evidence-based pharmacotherapy.^{30,31,48} The future of OA in T2DM will depend on four thresholds: reproducible systemic exposure, clinically relevant efficacy beyond standard care, acceptable long-term safety, and practical implementation. Current evidence supports continued investigation, not routine clinical use.^{9–11,37,38,44}

10. Conclusion

10.1. Short-term research value

Oleanolic acid is a biologically plausible investigational adjunct for T2DM. Preclinical studies link OA to insulin signaling, hepatic glucose production, oxidative stress, inflammation, lipid metabolism, and β -cell stress.^{4–7,14–23,34,35,47} Human data add two important translational signals: PREDIABOLE suggests prevention-oriented benefit in prediabetes, and BIO-OLTRAD shows that 30 mg OA delivered in functional olive oil can achieve measurable systemic exposure.^{9,10} These findings justify continued formulation-specific clinical testing, particularly in trials that connect exposure, pharmacodynamic biomarkers, glycemic endpoints, safety, adherence, and patient-reported outcomes.^{11,26,29–31}

10.2. Long-term clinical practicability

The long-term clinical role of OA remains uncertain. No completed large trial has yet established that OA improves HbA1c or other patient-relevant outcomes in established T2DM beyond standard care.^{2,3,9–11,26} Translation is limited by the small number of human studies, high doses and short durations in many animal models, uncertain exposure-response relationships, potential hepatic safety concerns,

regulatory restrictions on diabetes-related claims, and the practical burden of chronic oil intake.^{9–13,26,37,38,44,48,61,62,64–69} OA-enriched functional oil should therefore be framed as an investigational adjunct, not as an alternative to evidence-based pharmacotherapy.^{2,3,48} Clinical adoption would require reproducible benefit, acceptable hepatic and renal safety, compatibility with contemporary therapies, good tolerability, and feasible long-term use.^{2,3,25–31,37–39,44–46}

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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