

# Natural Products Targeting Insulin Resistance and $\beta$ -Cell Dysfunction in Type 2 Diabetes Mellitus: From Molecular Mechanisms to Clinical Translation

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## Abstract:

**Background:** Type 2 diabetes mellitus (T2DM) arises from the interaction of peripheral insulin resistance and progressive pancreatic  $\beta$ -cell dysfunction, both driven by overlapping mechanisms of glucotoxicity, lipotoxicity, chronic low-grade inflammation, oxidative stress, and endoplasmic-reticulum (ER) stress. Conventional pharmacotherapy, while effective, is limited by adherence, cost, and adverse-effect burden, sustaining strong scientific and clinical interest in natural products as adjunctive or complementary therapeutic agents. **Objective:** To synthesize current evidence on natural products acting on insulin resistance and  $\beta$ -cell dysfunction in T2DM, map their molecular mechanisms onto the signaling pathways that govern these two processes, critically grade the strength of pre-clinical versus clinical evidence for major compound classes, and outline priorities for clinical translation. **Methods:** A structured, non-systematic literature search of PubMed, Scopus, Web of Science, and Google Scholar (inception–June 2026) was conducted using combinations of compound-, condition-, and mechanism-specific search terms, detailed in Section 2. **Results:** Berberine, curcumin, and resveratrol possess the most substantial clinical-trial evidence base, with randomized controlled trials and meta-analyses demonstrating reductions in HOMA-IR, fasting glucose, and glycated hemoglobin (HbA1c), and, for curcumin specifically, direct evidence of improved  $\beta$ -cell function (HOMA- $\beta$ ) in a 12-month trial. Quercetin, mangiferin, puerarin, genistein, and related flavonoids/polyphenols show consistent mechanistic activity via AMPK, PI3K/Akt, Nrf2/HO-1, and NF- $\kappa$ B pathways in vitro and in animal models, but comparatively limited human trial data. A gut-microbiota–incretin axis, involving glucagon-like peptide-1 (GLP-1) secretion and short-chain fatty acid production, is increasingly implicated as a shared mechanism across compound classes. **Conclusion:** Natural products offer a mechanistically diverse, multi-target approach to insulin resistance and  $\beta$ -cell preservation in T2DM. Clinical translation is most advanced for berberine and curcumin; for most other compounds, standardized extract development, dose-ranging pharmacokinetic studies, and adequately powered clinical trials with direct  $\beta$ -cell functional endpoints (HOMA- $\beta$ , disposition index) remain priority needs.

**Keywords:** insulin resistance;  $\beta$ -cell dysfunction; type 2 diabetes mellitus; natural products; berberine; curcumin; resveratrol; AMPK; PI3K/Akt; Nrf2

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder defined by the combined presence of peripheral insulin resistance—reduced responsiveness of skeletal muscle, liver, and adipose tissue to insulin-mediated glucose disposal—and progressive dysfunction and eventual loss of insulin-secreting pancreatic  $\beta$ -cells. Neither defect alone is sufficient to produce overt hyperglycemia: compensatory  $\beta$ -cell hyperinsulinemia can maintain normoglycemia in the face of insulin resistance for years, and clinical diabetes typically emerges only once  $\beta$ -cell compensation fails. This dual pathophysiology—captured in the classical framework in which insulin resistance precedes, and  $\beta$ -cell dysfunction determines the timing and severity of, overt hyperglycemia—has made both processes independent and complementary therapeutic targets<sup>1-2</sup>.

Chronic exposure of insulin-target tissues and pancreatic islets to elevated glucose (glucotoxicity) and free fatty acids (lipotoxicity), together with chronic low-grade inflammation, oxidative stress, and ER stress, are now recognized as convergent upstream drivers of both peripheral insulin resistance and  $\beta$ -cell apoptosis/dysfunction. At the molecular level, impaired insulin receptor substrate (IRS)/phosphoinositide 3-kinase (PI3K)/Akt signaling and reduced GLUT4 translocation underlie peripheral insulin resistance, while NF- $\kappa$ B- and c-Jun N-terminal kinase (JNK)-mediated inflammatory signaling, ER stress markers (CHOP, GRP78), and oxidative damage converge on  $\beta$ -cell apoptosis and reduced insulin gene transcription (via PDX-1 suppression)<sup>3-4</sup>.

Current first-line and second-line pharmacotherapy for T2DM—metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists—target these pathways with substantial clinical benefit, but adherence challenges, cost, and drug-specific adverse effects (hypoglycemia, weight gain, gastrointestinal intolerance, genitourinary infection) continue to drive interest in complementary approaches. Natural products—plant- and microbially-derived small molecules including alkaloids (berberine), polyphenols (curcumin, resveratrol, quercetin), flavonoid glycosides (puerarin, genistein, mangiferin), and polysaccharides—have attracted particular attention because many act on multiple nodes of the insulin-resistance/ $\beta$ -cell-dysfunction network simultaneously, in a manner broadly analogous to (though generally less potent than) the multi-target action of metformin<sup>5-6</sup>.

### 1.1 Scope and Rationale of This Review

This review focuses specifically on natural products with documented activity at the molecular level relevant to insulin resistance and/or  $\beta$ -cell dysfunction in T2DM, deliberately excluding the broader and more heterogeneous category of plant extracts used traditionally for generic “blood sugar” lowering without mechanistic or target-specific data. It differs from prior broad-scope natural-product-and-diabetes reviews in two respects: first, it explicitly separates and compares the strength of clinical-trial evidence across compound classes (Section 6), rather than treating pre-clinical and clinical findings as equivalent; and second, it organizes

mechanistic discussion around the specific molecular distinction between insulin-resistance-directed pathways (IRS/PI3K/Akt, AMPK, GLUT4) and  $\beta$ -cell-directed pathways (PDX-1, ER stress, apoptosis regulators), reflecting the two-hit pathophysiological framework outlined above, with an additional dedicated treatment of the emerging gut-microbiota–incretin axis as a mechanism spanning both.

## 2. Literature Search Strategy

### 2.1 Databases and Time Period

PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched from database inception through June 2026, with particular attention to systematic reviews, meta-analyses, and randomized controlled trials (RCTs) published within the preceding five years to ensure currency of the clinical-evidence synthesis in Section 6.

### 2.2 Search Terms

Search strings combined three term clusters: (i) condition terms “type 2 diabetes”, “insulin resistance”, “ $\beta$ -cell dysfunction”, “beta cell dysfunction”, “HOMA-IR”, “HOMA- $\beta$ ”, “glucotoxicity”, “lipotoxicity”; (ii) compound terms “natural product”, “phytochemical”, “berberine”, “curcumin”, “resveratrol”, “quercetin”, “mangiferin”, “puerarin”, “genistein”, “polysaccharide”, “flavonoid”, “alkaloid”; and (iii) mechanism terms “AMPK”, “PI3K/Akt”, “IRS-1”, “GLUT4”, “NF- $\kappa$ B”, “JNK”, “Nrf2”, “ER stress”, “PDX-1”, “GLP-1”, “gut microbiota”, “randomized controlled trial”, “meta-analysis”.

### 2.3 Inclusion and Exclusion Criteria

- Included: peer-reviewed original research, systematic reviews, and meta-analyses published in English reporting mechanistic (in vitro/in vivo) or clinical (human RCT) data on a named natural product or defined extract in relation to insulin resistance,  $\beta$ -cell function/survival, or validated surrogate markers thereof (HOMA-IR, HOMA- $\beta$ , fasting insulin, glucose-stimulated insulin secretion, HbA1c).
- Excluded: non-peer-reviewed sources, studies of undefined or multi-herb formulations without individual compound attribution, conference abstracts without full data, and articles not available in English.

### 2.4 Evidence Grading Approach

For each major compound class discussed, this review explicitly distinguishes three evidence tiers, applied consistently in Section 6: (I) supported by human RCT and/or meta-analytic data with glycemic or insulin-resistance endpoints; (II) supported by consistent in vivo animal mechanistic data but limited or absent human trial data; (III) supported primarily by in vitro mechanistic data. This tiering is intended to give the reader an immediate, honest sense of translational maturity for each compound, rather than presenting all mechanistic findings as being of equivalent clinical relevance<sup>7-8</sup>.

### 3. Molecular Pathophysiology: A Framework for Mechanistic Discussion

#### 3.1 Peripheral Insulin Resistance

Insulin binding to its receptor normally triggers autophosphorylation and recruitment of insulin receptor substrate (IRS) proteins, activating the PI3K/Akt cascade that drives GLUT4 translocation to the plasma membrane (enabling glucose uptake in muscle and adipose tissue), glycogen synthase activation (promoting hepatic and muscle glycogen storage), and suppression of hepatic gluconeogenic enzymes (phosphoenolpyruvate carboxykinase [PEPCK], glucose-6-phosphatase [G6Pase]). In insulin resistance, chronic nutrient excess and adipose-tissue dysfunction drive serine (rather than tyrosine) phosphorylation of IRS-1 mediated substantially by JNK and IKK $\beta$ /NF- $\kappa$ B activation downstream of inflammatory and lipotoxic signaling impairing this cascade. AMP-activated protein kinase (AMPK), an energy-sensing kinase largely independent of the canonical insulin-receptor cascade, provides a parallel route to improved glucose uptake and reduced hepatic gluconeogenesis, and is a major convergent target for several natural products discussed below<sup>9-10</sup>.

#### 3.2 $\beta$ -Cell Dysfunction and Failure

Pancreatic  $\beta$ -cells respond to early insulin resistance with compensatory hyperplasia and increased insulin secretion. Sustained glucotoxicity and lipotoxicity, however, drive oxidative stress, ER stress (marked by CHOP and GRP78 upregulation), and mitochondrial dysfunction within  $\beta$ -cells, activating intrinsic apoptotic pathways and suppressing expression of pancreatic and duodenal homeobox 1 (PDX-1), the master transcription factor for insulin gene expression and  $\beta$ -cell identity maintenance. Chronic inflammatory cytokine exposure (IL-1 $\beta$ , TNF- $\alpha$ ) further amplifies  $\beta$ -cell NF- $\kappa$ B activation and apoptotic vulnerability. The net result is a progressive decline in functional  $\beta$ -cell mass and glucose-stimulated insulin secretion (GSIS) that, once advanced, is not fully reversible with current pharmacotherapy underscoring the clinical value of interventions capable of preserving  $\beta$ -cell function earlier in the disease course<sup>11-12</sup>.

#### 3.3 Shared and Converging Mechanisms

Oxidative stress and chronic low-grade inflammation are not confined to either tissue compartment but act as shared upstream drivers of both peripheral insulin resistance and  $\beta$ -cell dysfunction, providing the mechanistic rationale for natural products with combined antioxidant (typically Nrf2/HO-1-mediated) and anti-inflammatory (typically NF- $\kappa$ B/JNK-suppressing) activity to influence both processes concurrently, as opposed to synthetic agents that are more often selective for a single pathway (e.g., sulfonylureas for insulin secretion, thiazolidinediones for peripheral sensitivity)<sup>13-14</sup>.

### 4. Major Natural Product Classes: Overview

#### 4.1 Isoquinoline Alkaloids Berberine

Berberine, isolated from Berberis, Coptis, and related genera, is among the most extensively studied natural products in T2DM, with documented activity across AMPK activation, insulin-receptor upregulation, hepatic gluconeogenesis suppression, GLP-1 stimulation, and gut-

microbiota modulation, alongside anti-inflammatory and epigenetic-enzyme-targeting actions<sup>15</sup>.

#### 4.2 Curcuminoids Curcumin

Curcumin, the principal curcuminoid of *Curcuma longa*, has the most direct human evidence for  $\beta$ -cell functional preservation among natural products reviewed here, with a large ( $n = 272$ ), 12-month RCT demonstrating improved HOMA- $\beta$  alongside reduced HOMA-IR, fasting glucose, and HbA1c in obese T2DM patients, building on earlier trial evidence that curcumin can reduce progression from prediabetes to overt T2DM<sup>16</sup>.

#### 4.3 Stilbenes Resveratrol

Resveratrol, found in grapes, peanuts, and *Polygonum cuspidatum*, acts substantially through SIRT1 and AMPK activation and PI3K/Akt-pathway modulation; meta-analyses of RCTs indicate improved HOMA-IR and fasting glucose specifically in diabetic populations, with less consistent effects in non-diabetic subjects.

#### 4.4 Flavonoids and Flavonoid Glycosides Quercetin, Puerarin, Genistein, Hesperidin, Kaempferol

This structurally diverse group of dietary and traditional-medicine flavonoids has demonstrated activity across both insulin-resistance and  $\beta$ -cell-directed pathways in preclinical models including PI3K/Akt activation, GLUT4 upregulation, PDX-1 preservation, and suppression of ER stress and apoptotic markers in islets but, with some exceptions, has comparatively limited dedicated human RCT evidence in T2DM populations specifically<sup>17</sup>.

#### 4.5 Xanthonoids and Miscellaneous Polyphenols Mangiferin and Others

Mangiferin (from *Mangifera indica* and other sources) and related polyphenolic xanthonoids have documented antioxidant and PI3K/Akt-modulating activity in preclinical models relevant to both insulin sensitivity and  $\beta$ -cell protection, representing a mechanistically promising but clinically under-tested category.

#### 4.6 Polysaccharides

Plant- and fungal-derived polysaccharides (e.g., from *Dioscorea*, *Astragalus*, and related genera) have shown insulin-sensitizing and immunomodulatory activity in animal models and, in the case of astragalus polysaccharide, synergistic effects when combined with berberine, though standardization and human trial data remain limited relative to the alkaloid and polyphenol classes above<sup>18</sup>.

#### 4.7 Summary Table

Table 1 consolidates the compounds discussed above with their primary mechanistic targets, evidence tier (per Section 2.4), key findings, and source references.

| Natural Product / Class           | Primary Mechanistic Target(s)                                                                                                     | Evidence Type                                          | Key Clinical/Mechanistic Finding                                                                                                                                               | Reference |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Berberine (isoquinoline alkaloid) | AMPK activation; insulin-receptor upregulation; hepatic gluconeogenesis suppression; GLP-1 stimulation; gut microbiota modulation | Human RCT / meta-analysis (Tier I)                     | Enhances glucose-stimulated insulin secretion (phase 1 RCT, NCT03972215); combination with fenugreek reduced fasting insulin, HbA1c, hs-CRP, and HOMA-IR in a double-blind RCT | 19        |
| Curcumin (curcuminoid)            | HOMA- $\beta$ improvement; reduced serum free fatty acids; anti-inflammatory (CRP); insulin-resistance reduction                  | Human RCT (Tier I)                                     | 12-month, n = 272 RCT: significantly improved HOMA- $\beta$ , HOMA-IR, FPG, HbA1c, and body weight in obese T2DM patients                                                      | 20        |
| Curcumin (curcuminoid)            | $\beta$ -cell preservation; delayed progression to overt T2DM                                                                     | Human RCT (Tier I)                                     | 9-month RCT in prediabetes: 0% conversion to T2DM in curcumin group vs 16.4% in placebo group                                                                                  | 21        |
| Resveratrol (stilbene)            | SIRT1/AMPK activation; PI3K/Akt pathway modulation; anti-inflammatory (NF- $\kappa$ B)                                            | Human RCT meta-analysis (Tier I, diabetic populations) | Meta-analysis of RCTs: significant reduction in fasting plasma glucose, fasting insulin, and HOMA-IR in T2DM patients (effect not significant in non-diabetic subjects)        | 22        |

|                                                                            |                                                                                                                                      |                                       |                                                                                                                                                                                                             |    |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Quercetin,<br>kaempferol,<br>hesperidin,<br>luteolin<br>(flavonoids)       | PI3K/Akt/FOXO<br>signaling; PDX-<br>1 preservation;<br>ER-stress and<br>apoptosis<br>suppression in<br>islets; GLUT4<br>upregulation | In vitro /<br>animal (Tier<br>II–III) | Consistently activate<br>insulin-signaling and<br>$\beta$ -cell-protective<br>pathways across<br>multiple preclinical<br>models; human RCT<br>data in T2DM<br>populations<br>specifically remain<br>limited | 23 |
| Puerarin,<br>genistein,<br>geniposide<br>(flavonoid/iridoid<br>glycosides) | $\beta$ -cell<br>regeneration<br>promotion;<br>suppression of $\beta$ -<br>cell apoptosis<br>(FOXO, JNK,<br>mTOR<br>pathways)        | In vitro /<br>animal (Tier<br>II–III) | Preclinical evidence<br>for promoting islet $\beta$ -<br>cell regeneration and<br>inhibiting apoptosis<br>via multiple<br>convergent pathways                                                               | 24 |
| Mangiferin<br>(xanthonoid)                                                 | Antioxidant<br>(Nrf2/HO-1);<br>PI3K/Akt<br>modulation                                                                                | In vitro /<br>animal (Tier<br>II–III) | Documented<br>antioxidant and<br>insulin-sensitizing<br>activity in preclinical<br>models; dedicated<br>human T2DM RCTs<br>not identified                                                                   | 25 |
| Astragalus<br>polysaccharide +<br>berberine<br>(combination)               | Insulin-<br>resistance<br>amelioration<br>(combined<br>mechanism)                                                                    | Animal<br>model (Tier<br>II)          | Combination<br>produced<br>significantly greater<br>reductions in fasting<br>blood glucose and<br>insulin-resistance<br>index than either<br>monotherapy in<br>HFD-induced mice                             | 26 |

AMPK, AMP-activated protein kinase; CRP, C-reactive protein; FOXO, forkhead box class O; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; GLUT4, glucose transporter type 4; HbA1c, glycated hemoglobin; HFD, high-fat diet; HOMA-IR/HOMA- $\beta$ , homeostasis model assessment of insulin resistance/ $\beta$ -cell function; hs-CRP, high-sensitivity C-reactive protein; JNK, c-Jun N-terminal kinase; mTOR, mammalian target of rapamycin; NF- $\kappa$ B, nuclear factor kappa B; Nrf2/HO-1, nuclear factor erythroid 2-related factor 2/heme oxygenase-1; PDX-1, pancreatic and duodenal homeobox 1; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

## 5. Molecular Mechanisms: Insulin-Resistance and $\beta$ -Cell-Directed Pathways

### 5.1 AMPK and Peripheral Insulin Sensitization

AMPK activation the best-characterized mechanism for berberine and one of several proposed mechanisms for resveratrol and curcumin increases GLUT4-mediated glucose uptake in skeletal muscle, suppresses hepatic gluconeogenic gene expression (PEPCK, G6Pase), and promotes fatty-acid oxidation, collectively reducing peripheral and hepatic insulin resistance. For berberine specifically, this mechanism is supported by both preclinical pathway data and human RCT outcomes (reduced HOMA-IR, fasting insulin), representing one of the more directly evidenced mechanism-to-outcome links among the compounds reviewed<sup>27-28</sup>.

### 5.2 PI3K/Akt Signaling and GLUT4 Translocation

Multiple flavonoids (quercetin, kaempferol, genistein) and curcumin have demonstrated enhancement of PI3K/Akt pathway activity and downstream GLUT4 membrane translocation in cell and animal models, directly addressing the IRS-1/PI3K/Akt lesion characteristic of insulin-resistant states. Resveratrol's insulin-sensitizing effect has similarly been linked to PI3K-Akt pathway modulation, including via upregulation of specific microRNAs (e.g., miR-363-3p) shown to influence this pathway in mechanistic studies<sup>29-30</sup>.

### 5.3 $\beta$ -Cell Protection: ER Stress, Apoptosis, and PDX-1

Curcumin's demonstrated improvement in HOMA- $\beta$  in a large human RCT is mechanistically consistent with preclinical data showing curcumin and related polyphenols (resveratrol, genistein, puerarin, geniposide) reduce ER-stress markers (CHOP, GRP78) and pro-apoptotic signaling (JNK, FOXO-mediated pathways) in pancreatic  $\beta$ -cells, while preserving PDX-1 expression and, consequently, insulin gene transcription and glucose-stimulated insulin secretion. Resveratrol's  $\beta$ -cell protective activity has additionally been linked to SIRT1-mediated suppression of NF- $\kappa$ B-driven cytokine toxicity in islets<sup>31-32</sup>.

### 5.4 Nrf2/HO-1 Antioxidant Signaling and NF- $\kappa$ B/JNK-Mediated Inflammation

Given the convergent role of oxidative stress and inflammation in both insulin resistance and  $\beta$ -cell failure (Section 3.3), the Nrf2/HO-1 antioxidant axis and NF- $\kappa$ B/JNK inflammatory axis represent shared targets across nearly all compound classes reviewed. Resveratrol's anti-inflammatory activity, for example, operates substantially through SIRT1/NF- $\kappa$ B signaling and NF- $\kappa$ B/Nrf2 crosstalk, reducing COX-2 and iNOS expression; berberine similarly targets NF- $\kappa$ B to improve both insulin resistance and inflammation<sup>33-34</sup>.

### 5.5 Gut Microbiota–Incretin Axis

An increasingly recognized mechanism, particularly for berberine and dietary polyphenols more broadly, involves modulation of gut microbiota composition, short-chain fatty acid production, and stimulation of GLP-1 secretion from enteroendocrine L-cells, which in turn augments glucose-stimulated insulin secretion and may contribute to weight-related metabolic benefit. This axis is mechanistically plausible and increasingly documented for berberine

specifically, but remains comparatively less resolved in terms of direct causal human data for most other compounds in this review<sup>35</sup>.

## 5.6 Integrated Mechanistic Model

Figure 1 integrates the pathway-level discussion above into a single framework spanning peripheral insulin-signaling,  $\beta$ -cell function/survival, inflammation/oxidative stress, and the gut-microbiota–incretin axis, converging on the net metabolic outcome. As emphasized throughout, the strength of evidence underlying each arm of this framework varies substantially by compound (Section 6) and should not be read as uniformly established for every natural product discussed. Figure 1

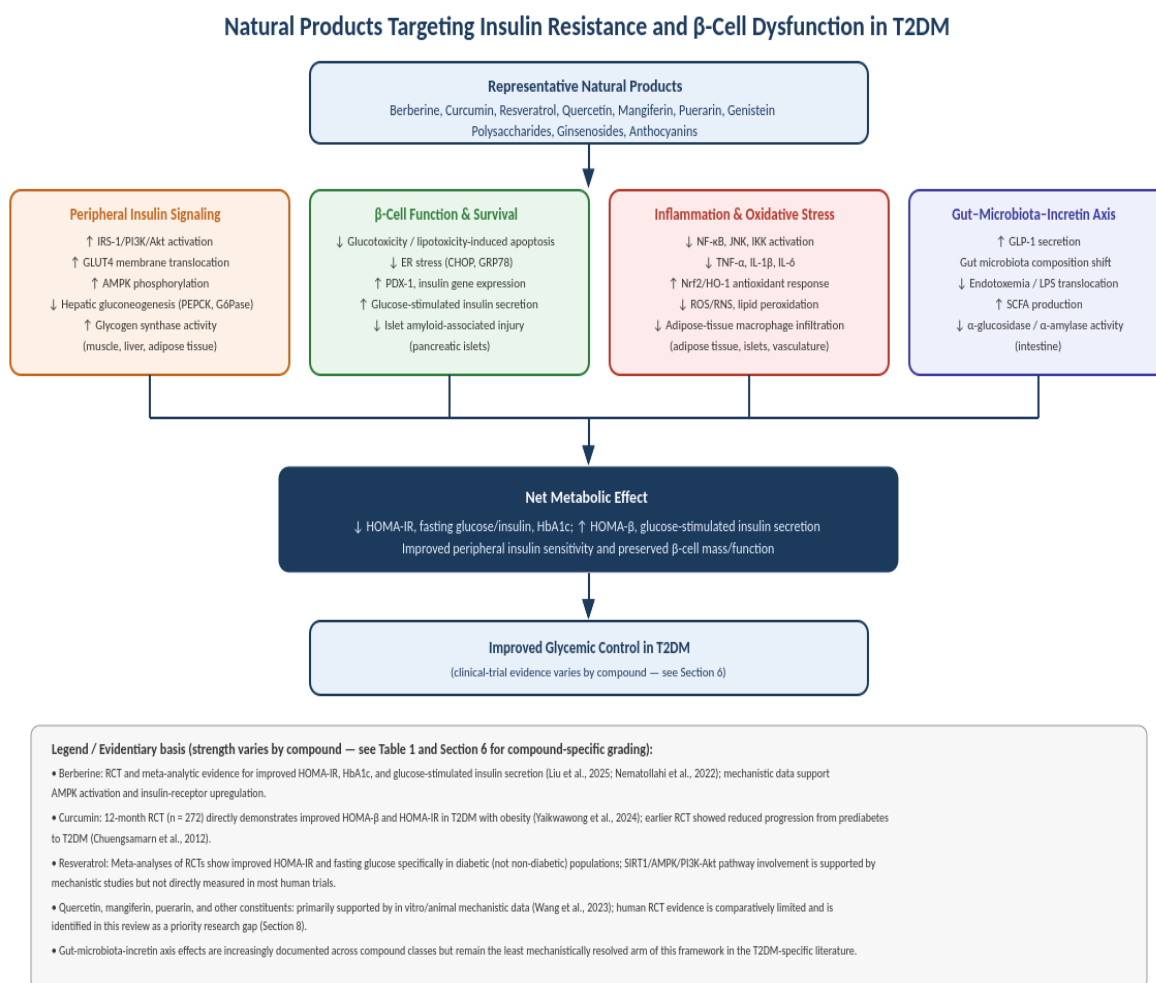


*Figure 1. Integrated mechanistic framework for natural products acting on peripheral insulin signaling,  $\beta$ -cell function/survival, inflammation/oxidative stress, and the gut-microbiota–incretin axis in type 2 diabetes mellitus. Evidence strength for each arm varies substantially by compound; see Section 6 for compound-specific grading.*

## 6. Critical Appraisal: Grading the Evidence by Compound

A central aim of this review is to avoid conflating mechanistic plausibility with clinical proof. Applying the three-tier grading approach defined in Section 2.4:

### 6.1 Tier I Human RCT / Meta-Analytic Evidence

Berberine, curcumin, and resveratrol meet Tier I criteria, with multiple RCTs and meta-analyses reporting statistically significant improvements in HOMA-IR, fasting glucose/insulin, and/or HbA1c in T2DM populations. Among these, only curcumin has direct RCT evidence of improved  $\beta$ -cell function specifically (via HOMA- $\beta$ ), representing the most mechanistically complete clinical evidence base among the compounds reviewed. Even within Tier I, however, important caveats apply: resveratrol's benefit appears specific to diabetic (versus non-diabetic) populations and effect sizes vary substantially across trials; berberine trials frequently combine it with other agents (fenugreek, metformin, astragalus polysaccharide), complicating attribution of effect to berberine alone in some studies; and heterogeneity in dose, formulation, and trial duration across the curcumin literature (1500 mg/day for 12 months in the largest trial identified) limits generalizability to other dosing regimens<sup>36-38</sup>.

### 6.2 Tier II Consistent Animal Model Evidence, Limited Human Data

Puerarin, genistein, geniposide, mangiferin, and astragalus polysaccharide fall into this tier: preclinical mechanistic and efficacy data are consistent and often detailed at the pathway level (specific kinases, transcription factors, and apoptotic markers identified), but dedicated, adequately powered human RCTs in T2DM populations were not identified for these compounds individually during this review's search.

### 6.3 Tier III Primarily In Vitro Mechanistic Evidence

Several individual flavonoids and phenolic acids (e.g., specific quercetin and kaempferol mechanistic findings) are supported predominantly by cell-culture data, with animal and human evidence either absent or not yet directly linking the in vitro mechanism to a whole-organism or clinical outcome<sup>39-40</sup>.

### 6.4 Cross-Cutting Limitations

- Standardization: extract and compound purity, dose, and formulation (e.g., berberine's inherently low oral bioavailability, addressed in some trials via co-formulation with ursodeoxycholic acid) vary considerably across studies, limiting cross-trial comparability.
- Comparator design: many RCTs compare natural products to placebo rather than to standard-of-care agents (metformin, GLP-1 receptor agonists), limiting inference about relative, as opposed to absolute, efficacy.
- Endpoint selection: HOMA-IR and HOMA- $\beta$  are validated but indirect surrogate measures; few trials employ gold-standard techniques (hyperinsulinemic-euglycemic clamp for insulin sensitivity, or disposition index/arginine-stimulation testing for  $\beta$ -cell function) that would provide more definitive mechanistic confirmation.

- Publication and language bias: several meta-analyses draw substantially on the Chinese-language literature for berberine and resveratrol; while informative, this raises the standard methodological considerations around database coverage and potential publication bias that should be borne in mind when interpreting pooled effect sizes.

## 7. Translational Relevance

### 7.1 Pharmacokinetics and Bioavailability

Poor oral bioavailability is a well-documented, compound-specific barrier: berberine undergoes extensive first-pass metabolism and P-glycoprotein-mediated efflux, motivating novel formulations such as berberine ursodeoxycholate (currently in phase 2 clinical evaluation, NCT06411275) designed to enhance systemic exposure; curcumin's bioavailability is likewise low and typically addressed via piperine co-administration, nanoparticle, or phospholipid-complex formulations; resveratrol undergoes rapid glucuronidation and sulfation, substantially limiting free systemic exposure despite good absorption. Bioavailability-enhancing formulation strategies should therefore be considered a prerequisite, rather than an optional refinement, for translating in vitro potency into clinical effect for these compound classes<sup>41-42</sup>.

### 7.2 Safety and Tolerability

Berberine and curcumin have generally favourable safety profiles at studied clinical doses, with gastrointestinal effects (diarrhea, constipation) the most commonly reported adverse events for berberine, and mild gastrointestinal upset occasionally reported for curcumin; meta-analytic data for berberine specifically report no signal for renal toxicity at standard dosing (0.6–1.5 g/day). Resveratrol has been generally well tolerated in trials to date, though data in special populations (pregnancy, renal/hepatic impairment) remain limited. Systematic long-term (multi-year) safety data are comparatively sparse for all three compounds relative to established pharmacotherapy, and are essentially absent for the Tier II/III compounds discussed in Section 6.2–6.3<sup>43-44</sup>.

### 7.3 Dosage Considerations

Clinically studied dose ranges vary substantially by compound: berberine trials commonly use 0.6–1.5 g/day in divided doses; the largest curcumin  $\beta$ -cell trial used 1500 mg/day of a standardized extract for 12 months; resveratrol trial doses have ranged widely (commonly 150 mg/day to 1 g/day) across studies included in meta-analyses, contributing to between-trial heterogeneity. Dose standardization against a defined marker-compound content, and head-to-head dose-ranging studies, remain a priority for all three Tier I compounds and are essentially unaddressed for Tier II/III compounds<sup>45-46</sup>.

### 7.4 Herb–Drug Interactions

Berberine is a recognized inhibitor of several cytochrome P450 isoforms (notably CYP2D6 and CYP3A4) and can increase plasma concentrations of co-administered substrates including some statins and calcium-channel blockers; combination with metformin (a common co-

administration pattern in the reviewed literature) has generally been reported as safe and synergistic but warrants monitoring for additive gastrointestinal effects. Curcumin and resveratrol are similarly recognized CYP3A4-pathway modulators, raising theoretical interaction potential with a range of concomitant medications; dedicated interaction studies specific to T2DM polypharmacy (including sulfonylureas and insulin, where additive hypoglycemic risk is a specific concern) remain limited and should be a focus of future clinical research<sup>47</sup>.

## 7.5 Current Status of Clinical Development

Berberine, in the novel co-formulation berberine ursodeoxycholate (HTD1801), is furthest along a formal regulatory development pathway, with an ongoing phase 2 trial (NCT06411275) in patients with T2DM inadequately controlled by diet and exercise. Curcumin and resveratrol, despite a substantial existing RCT base, remain positioned as dietary-supplement-level interventions rather than agents pursuing formal drug regulatory approval for T2DM at this time. Tier II/III compounds remain, at present, exclusively at the pre-clinical stage of development for this specific indication.

## 8. Future Perspectives and Research Priorities

### 8.1 Direct $\beta$ -Cell Functional Endpoints

Future clinical trials of natural products in T2DM should prioritize direct measures of  $\beta$ -cell function (HOMA- $\beta$ , disposition index, arginine-stimulation or mixed-meal-stimulated C-peptide response) rather than relying solely on glycemic surrogates, following the model set by the 2024 curcumin trial, to establish whether other Tier I/II compounds similarly preserve  $\beta$ -cell function rather than acting exclusively through peripheral insulin sensitization<sup>48</sup>.

### 8.2 Bioavailability-Optimized Formulations

Given the well-documented bioavailability limitations of berberine, curcumin, and resveratrol (Section 7.1), continued development and head-to-head clinical comparison of enhanced-bioavailability formulations (co-crystals, nanoparticle/liposomal delivery, novel bile-acid conjugates such as berberine ursodeoxycholate) should be prioritized over further studies of unmodified compounds at conventional doses.

### 8.3 Advancement of Tier II/III Compounds

Puerarin, genistein, geniposide, mangiferin, and structurally related flavonoids/xanthonoids warrant dedicated, adequately powered human RCTs with glycemic and  $\beta$ -cell functional endpoints to determine whether their consistent preclinical mechanistic profile translates to clinical benefit, addressing the principal evidence gap identified in Section 6.2<sup>49</sup>.

### 8.4 Head-to-Head and Combination Trials

Given the frequent co-administration of natural products with standard pharmacotherapy (notably berberine with metformin, and berberine with astragalus polysaccharide or fenugreek) observed in the existing literature, well-designed combination and head-to-head comparator

trials rather than exclusively placebo-controlled designs would better establish the incremental or synergistic clinical value of these agents relative to, and alongside, established T2DM pharmacotherapy.

### 8.5 Omics and Gut-Microbiota Mechanistic Studies

Given the emerging but still incompletely resolved role of the gut-microbiota–incretin axis (Section 5.5), metagenomic and metabolomic profiling alongside GLP-1 and short-chain fatty acid measurement in future human trials would help clarify the relative contribution of this mechanism versus direct tissue-level pathway effects across compound classes.

### 8.6 Long-Term Safety Data

Multi-year pharmacovigilance and safety follow-up, particularly for combination regimens involving natural products alongside standard pharmacotherapy, is needed to complement the largely short-to-medium-term (weeks to 12 months) trial durations that currently dominate the evidence base<sup>50</sup>.

## 9. Conclusion

Natural products offer a mechanistically diverse, multi-target complement to conventional T2DM pharmacotherapy, with documented activity spanning peripheral insulin-signaling pathways (AMPK, IRS-1/PI3K/Akt, GLUT4),  $\beta$ -cell-protective pathways (ER-stress and apoptosis suppression, PDX-1 preservation), shared anti-inflammatory/antioxidant mechanisms (NF- $\kappa$ B/JNK suppression, Nrf2/HO-1 activation), and an emerging gut-microbiota–incretin axis. Clinical translation, however, is markedly uneven across compounds: berberine, curcumin, and resveratrol are supported by meaningful human RCT and meta-analytic evidence, with curcumin uniquely demonstrating direct  $\beta$ -cell functional benefit in a large trial, while most other mechanistically promising compounds including puerarin, genistein, mangiferin, and related flavonoids remain at the preclinical stage for this specific indication. Honest, compound-specific evidence grading, of the kind applied throughout this review, is essential to guide both future research investment and any clinical communication about the present-day role of natural products in T2DM management: as an increasingly well-supported adjunct for a small number of compounds, and as a promising but still unproven research direction for the majority.

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