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Review

Functional Foods and Bioactive Compounds in Managing Type 2 Diabetes Through Nutrigenomics

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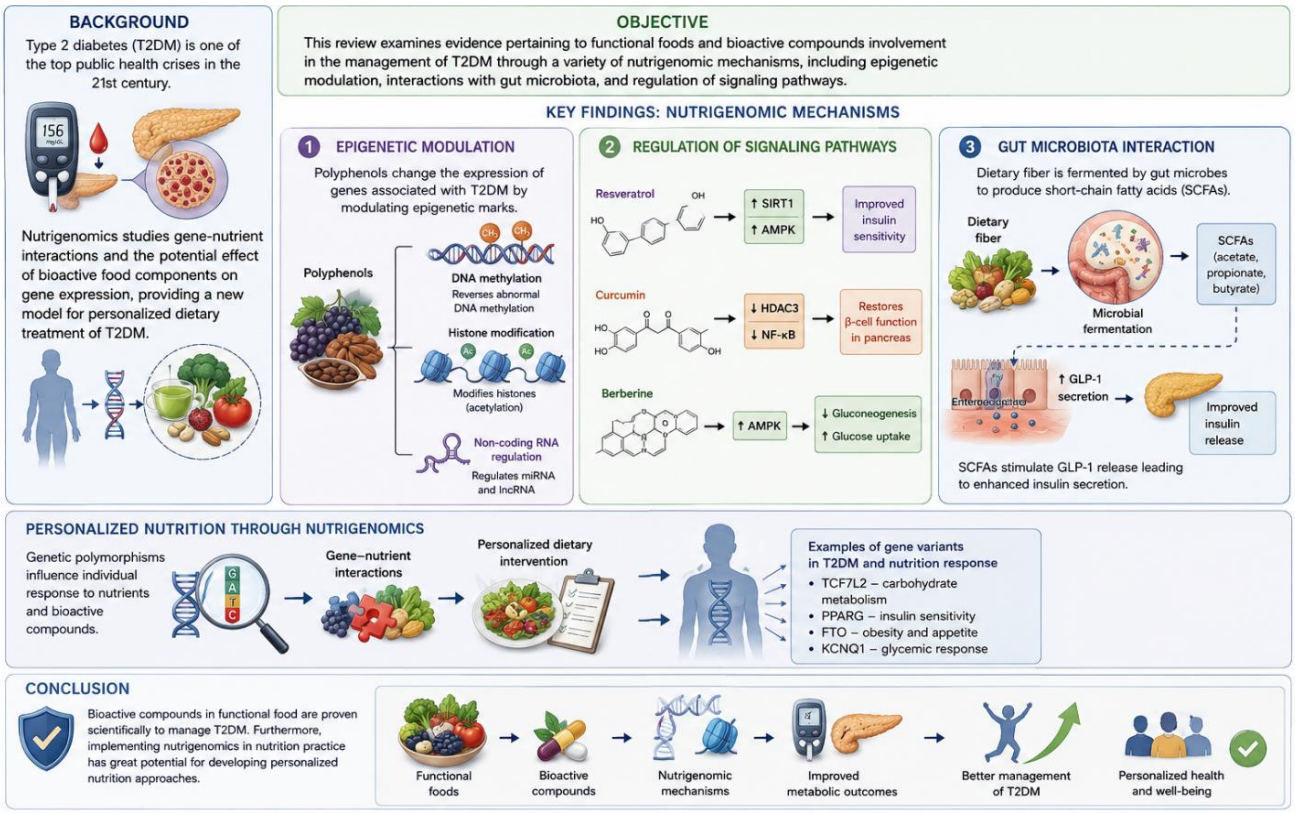
Abstract:
Type 2 diabetes mellitus (T2DM) represents a major global health challenge driven by insulin resistance, β-cell dysfunction, chronic inflammation, oxidative stress, and gut dysbiosis. This review explores the emerging role of nutrigenomics in T2DM management, focusing on how functional foods and their bioactive compounds modulate gene expression, epigenetic mechanisms, and metabolic pathways to improve glycemic control. Key bioactive compounds (including resveratrol, curcumin, quercetin, genistein, berberine, EGCG, and omega-3 PUFAs) exert pleiotropic effects through activation of AMPK and SIRT1, inhibition of NF-κB, modulation of DNA methylation and histone acetylation, regulation of miRNAs, and enhancement of gut microbiota-derived short-chain fatty acids (SCFAs) such as butyrate. These actions collectively improve insulin sensitivity, protect β-cells, reduce inflammation, and restore metabolic homeostasis. Clinical evidence from randomized controlled trials and meta-analyses demonstrates significant reductions in fasting blood glucose, HbA1c, and HOMA-IR, with some compounds (such as curcumin) showing preventive efficacy in prediabetes. Despite challenges related to bioavailability and inter-individual genetic variation, advances in precision nutrition, multi-omics profiling, and formulation technologies position functional foods as a sustainable, mechanism-based complement to conventional pharmacotherapy. This nutrigenomic framework highlights the paradigm of "food as medicine" and underscores the need for personalized dietary interventions to combat the T2DM epidemic.

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Graphical Abstract



1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, multifactorial disorder caused by progressively developing insulin resistance with associated pancreatic β-cell malfunction and eventual sustained high blood sugar or glucose levels. T2DM is the most common type of diabetes, representing >90% of all diabetes cases throughout the world today [1]. According to data included in the most recent (11th) Edition of the International Diabetes Federation (IDF) Diabetes Atlas, it is estimated that approximately 537 million adults between the ages of 20 and 79 have diabetes, approximately 10.5% of the global adult population [2,3]. This number is expected to grow to 643 million by 2030 and 783 million by 2045, with prevalence rates expected to exceed 12.8% by the middle of the century [3,4]. Therefore, there is a pressing need for these management strategies to be effective, accessible, and sustainable [1]. Genetic susceptibility, epigenetic change, dietary habits, lifestyle choices, and gut microbiome composition all play a role in the development of T2DM [5,6]. Although pharmacological treatments (including metformin, sulfonylureas, SGLT2 inhibitors, and GLP-1 receptor agonists) are effective therapies for helping patients control their blood sugar levels; however, they also have significant limitations such as side effects, high costs, and inability to address the underlying diet-related or genetic causes of T2DM [7].

Nutrigenomics is a science that studies the interaction between dietary nutrients, bioactive components of food and how they can affect gene expression by interacting with the genome. Therefore, it provides an exciting addition to existing ways of managing T2DM. Through the study of gene-diet interactions, nutrigenomics enables development of personalized diets based on an individual's unique genetic profile, metabolic and microbiome make up [8,9]. By moving away from 'one-size-fits-all' dietary guidance and instead providing precision nutritional intervention for each person with diabetes represents the new frontier in diabetes treatment. Functional foods, defined by international bodies such as the European Food Safety Authority (EFSA), the US Food and Drug

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Administration (FDA), and the World Health Organization (WHO) as foods containing bioactive components providing health benefits beyond basic nutritional value, have garnered significant scientific and clinical attention [10]. These foods contain bioactive components, including polyphenolic compounds, dietary fiber, omega-3 polyunsaturated fatty acids (PUFAs), vitamins and alkaloid. In addition, many of these compounds can help modulate metabolic pathways that are associated with the development of T2DM [8,11].

Several very well studied bioactive compounds including curcumin, resveratrol, berberine, quercetin, genistein, and epigallocatechin gallate (EGCG) have been evaluated for their potential to increase insulin sensitivity, reduce chronic inflammation, protect pancreatic β-cells, and negatively regulate major signaling pathways (such as AMPK, NF-κB, SIRT1 and PI3K/Akt) [6,8,12]. Additionally, the interaction between dietary components and the gut microbiota generates short-chain fatty acids (SCFAs) and other metabolites that exert profound effects on glucose homeostasis and insulin signaling [13,14]. This review will provide a synthesis of evidence to support T2DM management with the use of functional foods/bioactive compounds that operate through nutrigenomic mechanisms. We aim to establish a theoretical framework of nutrigenomics regarding T2DM, to classify functional foods and their bioactive constituents, to detail how specific bioactive compounds work, and to evaluate the potential impact of gut microbiota on these compounds.

2. Nutrigenomics and Type 2 Diabetes

Nutrigenomics is based on the belief that dietary components are not just energy sources; they act as molecular signals that communicate with genes to affect gene expression, protein synthesis, and produce metabolites [9,15]. Nutrigenomics differs from nutrigenetics that investigates how genetic variations (most commonly Single Nucleotide Polymorphisms) influence the absorption, metabolism, and utilization of nutrients [16]. The discipline encompasses several interrelated areas (Figure 1): transcriptomics (diet-induced changes in mRNA expression), proteomics (alterations in protein profiles), metabolomics (changes in metabolite concentrations), and epigenomics (heritable modifications in gene expression not involving DNA sequence changes) [17].

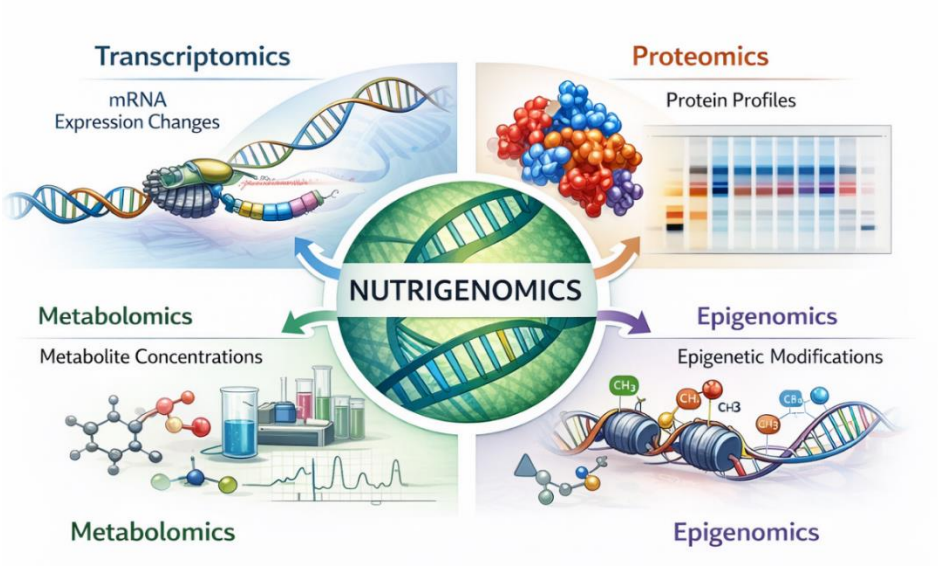


Figure 1. Integrative Omics Approaches in Nutrigenomics. The schematic illustrates the four main pillars of nutrigenomics: transcriptomics (diet-induced changes in mRNA expression), proteomics (alterations in protein profiles and functions), metabolomics (changes in metabolite levels and metabolic pathways), and epigenomics (diet-induced modifications such as DNA methylation and histone changes). Together, these integrated omics fields

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reveal how nutrition influences gene expression, proteins, and metabolism. Created with Mindthegraph (https://mindthegraph.com/).

In the context of T2DM, pathogenesis involves complex interactions among genetic factors, epigenetic modifications, and environmental triggers, especially diet (Table 1). Nutrigenetic studies look at the role of genetic variations (polymorphisms) in influencing individual differences in response to diet, while nutrigenomics focuses on how certain nutrients and bioactive substances affect the expression of genes that relate to diabetes [18]. For example, some polymorphisms in PPAR-gamma, TCF7L2, FTO, and IRS-1 have been implicated in the differences in susceptibility to insulin resistance due to diet effects [19].

Table 1. Major nutrigenomic themes and evidence gaps in T2DM

Theme / Area	What is relatively well-supported	Key gaps / needs
Gene–diet interactions in T2D risk	Multiple SNP–diet interactions (PPARG, TCF7L2, FTO, others) linked to insulin resistance, obesity, and glycaemia	Large, diverse, longitudinal cohorts to quantify effect sizes and refine who benefits from which diet
Bioactives (polyphenols, carotenoids, etc.)	Modulate expression of genes controlling oxidative stress, inflammation, lipid and glucose metabolism; improve markers in models and small trials	Dose–response, long-term safety, and definitive clinical outcome trials in humans with T2DM
Microbiome and metabolomics	Diet-induced changes in microbial and metabolic profiles linked to glycaemic control and insulin resistance; prediction models emerging	Causal pathways, scalable phenotyping, integration into routine care and guidelines
Clinical precision nutrition	Early trials show improved surrogate cardiometabolic outcomes when stratifying by genotype or metabotype	Large randomized controlled trials (RCTs) comparing gene/omics-tailored diets with standard high-quality diets on T2DM incidence/complications

2.1 Epigenetic Modifications in T2DM

The interface between epigenetic mechanisms and environmental exposure, like nutrition and gene transcription, is important. In association with T2DM, many studies have been conducted on the effects of three main epigenetic mechanisms; DNA methylation, histone modification, and non-coding RNA regulation [5,20]. DNA methylation is a process through which methyl groups are added to cytosine bases in CpG dimer units, which results in silencing genes. In T2DM, aberrant DNA methylation has been linked to alterations in methylation levels of several genes including PDX1 (the gene that encodes for a transcription factor critical for insulin production), INS, and GLUT4 [5].

The modifications made to histones, such as acetylation, methylation, ubiquination and phosphorylation, are factors that affect how DNA is packed (i.e., the structure of chromatin), as well as how easy it is for transcription factors to bind with gene promoters. Hyperacetylation of histones at the promoters of pro-inflammatory genes (i.e. those of NF-kB) is one well-known characteristic of 'diabetic metabolic memory' [11,12]. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are two types of non-coding RNAs (ncRNAs) that are important for regulating how genes are expressed after transcription, which is important for T2DM. Some of the miRNAs that help to regulate insulin signaling and the function of pancreatic β-cells include miR-21, miR-34a, miR-146a, and miR-375 [21].

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2.2 The Nutrigenomics-Precision Nutrition Nexus

The use of Omics technologies combined with nutrigenomics has significantly enhanced the ability to understand how dietary intake modifies the molecular processes of T2DM pathophysiology, Figure 2 [22]. The use of multomics techniques allows for the complete profile of individual metabolic responses to dietary treatments, resulting in much more effective personalized nutritional guidelines than population-based nutritional guidelines [23].

Foodomics is the use of cutting-edge analytical and bioinformatics methods to understand the effects of food and its component parts on human health at an omics level. Foodomics is an exciting area of research because it can combine metabolomic data with proteomic and genomic data to provide insight into how a person might respond to specific functional foods or bioactive compounds, facilitating precision nutrition interventions in T2DM [17,24].

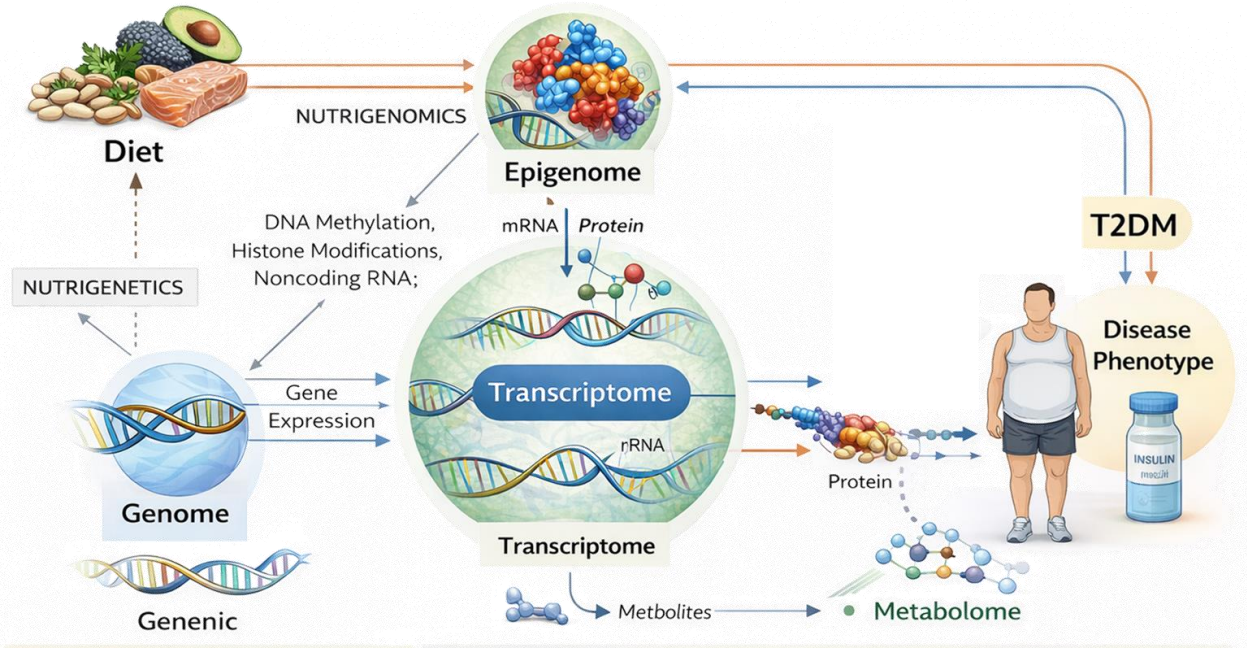


Figure 2. Interaction between diet, epigenome, genome, transcriptome, proteome, metabolome, and disease phenotype in T2DM, showing the nutrigenetics-nutrigenomics interactive model. Dietary components, particularly nutraceuticals from foods, modify the genome via nutrigenomic pathways (DNA methylation, histone modifications, non-coding RNAs, and epigenome). Changes at this level affect gene expression and the transcript (transcriptome), thereby changing the levels of proteins (proteome) and metabolites (metabolome). This ultimately impacts the disease phenotype. Arrows depict causal flows from diet to molecular layers (genome, epigenome, transcriptome, proteome, metabolome) and outward to observable phenotypes. Created with Mindthegraph (https://mindthegraph.com/).

3. Functional Foods: Classification and Bioactive Constituents

Functional foods are generally described as foods which, in addition to their primary nutritional benefit, provide measurable physiological effects and/or reduce the likelihood of developing chronic disease, when included with a balanced diet [10]. Functional foods are widely accepted by international regulatory authorities like the European Food Safety Authority (EFSA), U.S. Food and Drug Administration (FDA) and World Health Organization (WHO) to have bioactive substances, which can help to prevent or treat the occurrence of chronic,

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non-communicable diseases (NCDs) such as T2DM. Bioactive compound are substance that occur naturally in food and have benefits beyond basic nutrition. They exist in all different sources of food (plants, animals, fungi and bacteria) and when ingested at sufficient levels can interact with the human genome, alter cellular metabolic pathways and give health benefits beyond basic nutrition [25]. Functional foods used for T2DM can be categorized by their origin of food source or class of bioactive compound predominates in the metabolically active food. The primary mechanisms of action for these compounds are increased insulin sensitivity, reduced postprandial glycaemia, and antioxidant/anti-inflammation activities on blood sugar metabolism as outlined in Table 2.

Table 2. Classification and Primary Anti-Diabetic Actions of Functional Food Categories

Category	Food Sources	Key Bioactive Compounds	Primary Anti-Diabetic Action
Phytochemicals	Fruits, vegetables, legumes, spices, whole grains	Polyphenols, flavonoids, carotenoids, glucosinolates, curcuminoids	Antioxidant, anti-inflammatory, insulin sensitizing, gene expression modulation [6,8].
Zoochemicals	Fatty fish, fish oil, egg yolk, dairy	Omega-3 PUFAs, conjugated linoleic acid, vitamin D	AMPK activation, PPAR-γ modulation, ER stress inhibition, inflammation reduction [6,26].
Macrofungi-derived	Mushrooms (*Ganoderma lucidum*, *Lentinula edodes*, *Grifola frondosa*)	β-glucans, polysaccharides, terpenoids	Gut microbiota modulation, α-glucosidase inhibition, glucose uptake enhancement [8,27].
Fermented foods	Yogurt, kefir, kimchi, sauerkraut, miso	Probiotics, bioactive peptides, GABA	Gut microbiome restoration, SCFA production, incretin secretion [13,28].
Plant alkaloids	*Berberis vulgaris*, goldenseal, tree turmeric	Berberine, protoberberine alkaloids	AMPK activation, gluconeogenesis inhibition, gut microbiota modulation [29,30].
Dietary fibre	Oats (*Avena sativa*), barley, legumes, psyllium, chicory	β-glucan, inulin, pectin, resistant starch, fructooligosaccharides	SCFA production, GLP-1 stimulation, glucose absorption reduction, satiety [13,14,31].

4. Molecular Mechanisms of Bioactive Compounds in T2DM Management

4.1 Polyphenols and Gene Expression Modulation

The major focus of research on bioactive compounds with respect to T2DM and nutrigenomics has been polyphenols due to their large number of studies completed thus far. Polyphenols are secondary metabolites that can be found in nearly all foods classified as being from either a fruit or vegetable source, tea, wine, coffee and chocolate and therefore represent a very broad class of structure types through flavonoids, phenolic acids, stilbenes, lignans and curcuminoids [8]. Their anti-diabetic activity is mediated through a constellation of mechanisms, including the modulation of genes involved in glucose and lipid metabolism, insulin signalling, oxidative stress response, and inflammatory pathways.

The expression of many genes essential to T2DM pathophysiology has been demonstrated to be regulated by polyphenols from in vitro, in vivo, and clinical data. The genes regulated include those for GLUT4 (glucose transporter type 4), IRS-1 (insulin receptor substrate 1), PPAR-gamma, FOXO1 (Forkhead box Protein O1), and key enzymes involved with gluconeogenesis (such as G6Pase (Glucose-6-Phosphate) and PEPCK (Phosphoenolpyruvate Carboxykinase)). The pleiotropic effects of polyphenols promote weight control, glycemic control, insulin resistance reduction and the protection of pancreatic β-cells against apoptosis by modulating these gene targets [6,9,32–38].

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Carbohydrate breakdown processes are inhibited by polyphenols through their ability to inhibit the activity of the major carbohydrate-digesting enzymes, namely alpha-glucosidase and alpha-amylase. Several dietary polyphenols, such as catechins, quercetin, and chlorogenic acid exhibit substantial inhibition of alpha-glucosidase and alpha-amylase activity and thus decrease postprandial hyperglycemia by delaying carbohydrate digestion and glucose absorption [8,25]. In addition to providing an alternative method of glycemic control at the genomic level through regulation of gene expression, this inhibition of carbohydrate digestion and absorption creates a multi-faceted strategy for managing glycemia.

4.2 Epigenetic Mechanisms: DNA Methylation and Histone Modification

Nutrigenomics research represents one of the most important and most complex epigenetic modulations of the diabetes-associated gene group by dietary polyphenols [5]. In contrast to traditional pharmacological agents that typically have a single pathway of action, bioactive compounds (resveratrol, curcumin, quercetin, EGCG) appear to be able to modulate multiple, interconnected epigenetic mechanisms.

The direct interaction between curcumin and the enzyme HDAC, mostly HDAC3, results in increased levels of acetylated histones at metabolic gene promoters [39]. This activity creates an environment conducive to the re-establishment of previously silenced insulin and PDX-1 (homeobox 1), and other transcription factors that have become faulty in diabetic progression. In addition to selectively inhibiting HDAC1, curcumin modulates histone acetyltransferase (HAT) activity, therefore producing a balanced regulatory effect on the chromatin's structure. By inhibiting DNMT (DNA methyltransferase), curcumin reverses the hypermethylation of key metabolic gene promoters thus restoring normal patterns of gene expression [12,40].

Grapes and red wine have resveratrol that acts through the dual epigenetic mechanism: stimulating SIRT1 (Sirtuin-1) that is a class III histone deacetylase and inhibiting both class I and II HDACs. The SIRT1 activity increases deacetylation of FOXO1 and PGC-1alpha, which enhances both mitochondrial biogenesis, fatty acid oxidation, and insulin sensitivity in muscle tissue. In addition, resveratrol is currently in Phase II clinical trials for the treatment of diabetes and obesity with demonstrated results on mitochondrial biogenesis and improvements in metabolism [6,12].

Quercetin regulates epigenetic modifications by blocking the activity of DNA methyltransferases (DNMT), which leads to demethylation and reactivation of insulin signaling genes [11]. Quercetin also inhibits JNK signaling in lipopolysaccharide (LPS)-stimulated macrophages, which reduce iNOS and COX-2 expression, a key mechanism in chronic low-grade inflammation that persists insulin resistance in T2DM [25]. Genistein, an isoflavone from soybeans, enhances the proliferation of pancreatic β-cells and increases insulin production by increasing expression levels of transcription factors PDX-1 and Nkx6.1. Genistein's ability to reverse insulin gene promoter methylation status, leading to restored insulin expression in β-cells of T2DM patients is a result of epigenetic actions [6,9].

4.3 Non-Coding RNA Regulation

miRNA, a small non-protein coding RNA molecule (~22 nucleotides long), can regulate how genes are expressed after they have been transcribed, by binding to the 3' UTR of the target mRNA Transcript. Evidence has accumulated to show that dietary polyphenols can alter miRNA expression profile related to T2DM [20,21]. miR-34a, a miRNA associated with β-cell apoptosis and impaired insulin secretion, may be downregulated by resveratrol and same resveratrol also upregulates miR-200a, which provides protection against oxidative stress-induced β-cell death [20]. miR-21 are modulated by curcumin decreasing its pro-inflammatory effects on the NF-κB pathway in models of diabetic retinopathy and nephropathy [40].

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Resveratrol downregulates miR-34a (a miRNA associated with β-cell apoptosis and impaired insulin secretion) while upregulating miR-200a, implicated in protection against oxidative stress-induced β-cell death [20]. Curcumin modulates miR-21, reducing its pro-inflammatory effects on the NF-κB pathway in diabetic retinopathy and nephropathy models [40]. Green tea's EGCG regulates the miR-126/VEGF pathways, affecting complications associated with diabetes through microvasculature [21]. lncRNAs have been recognized as epigenetic regulators in T2DM; thus, curcumin and resveratrol alter expression of these types of RNAs found in pancreatic β-cells and liver cells, both of which can modulate insulin gene transcription and gluconeogenic programming within those tissues [5].

4.4 AMPK Signaling Pathway Activation

AMP-activated protein kinase (AMPK) regulates energy levels in cells via metabolic sensor signaling pathways. T2DM typically exhibits reduced AMPK activity, leading to increased gluconeogenesis (increased production of glucose) and decreased glucose uptake by cells, which in turn leads to increased fat production (lipogenesis). As a result, there are many bioactive compounds that activate AMPK directly through different mechanisms, making this signaling pathway an important target for functional food-based interventions in managing T2DM, Figure 3 [41]. Bioactive compounds when they activate AMPK, produce an overall metabolic response which includes: (i) increased glucose transport into plasma membrane via GLUT4 translocation; (ii) increased fat metabolism due to stimulation of fatty acid oxidation via CPT-1 (carnitine palmitoyltransferase-1) activation; (iv) decreased gluconeogenesis due to suppression of PEPCK and G6Pase; (v) decreased lipogenesis due to inhibition of SREBP-1c; (vi) improved insulin sensitivity; reduced apoptosis of β-cell; (vii) reduced oxidative stress; and (viii) reduced production of inflammatory cytokine production [30].

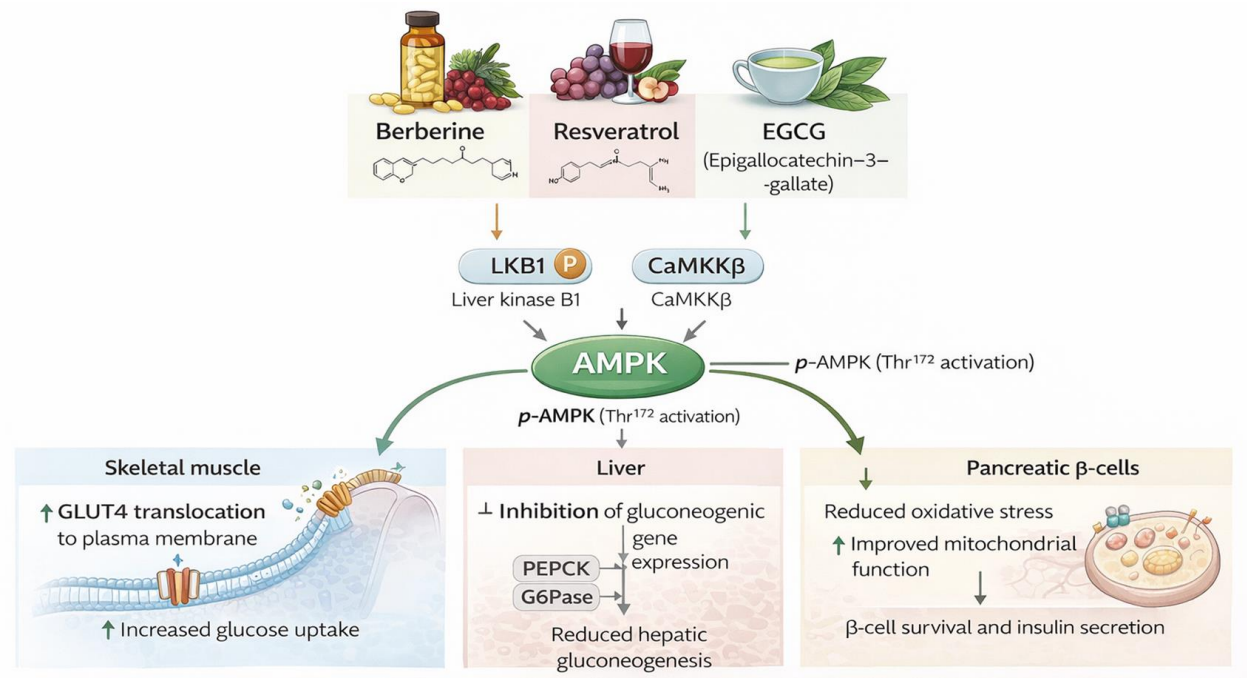


Figure 3. AMPK-mediated metabolic effects of natural polyphenols. Berberine, resveratrol and EGCG activate AMPK in liver cells via upstream kinases such as LKB1 and CaMKKβ. This activation inhibits mTORC1 while promoting p-AMPK^(Thr172) phosphorylation, leading to enhanced glucose uptake in skeletal muscle through increased GLUT4 translocation to the plasma membrane, suppressed hepatic gluconeogenesis via reduced expression of key gluconeogenic genes (such as PEPCK), and improved pancreatic β-cell function with boosted mitochondrial oxidative stress resistance and insulin secretion. Arrows depict activation (green) or inhibition (red);

cellular compartments and molecular targets are labeled accordingly. Abbreviations: Liver kinase B1 (LKB1) and Ca^{2+}/calmodulin-dependent protein kinase kinase-β (CaMKKβ), mammalian target of rapamycin complex 1 (mTORC1). Created with Mindthegraph (https://mindthegraph.com/).

The diverse molecular mechanisms through which these bioactive compounds exert their nutrigenomic effects, ranging from epigenetic modifications to the activation of central metabolic sensors, are synthesized in Table 3.

Table 3. Summary of Major Nutrigenomic Mechanisms and Associated Bioactive Compounds in T2DM Management

Nutrigenomic Mechanism	Bioactive Compound(s)	Primary Molecular Targets	Biological Outcome
DNA Methylation Regulation	Quercetin, EGCG, Curcumin, Genistein, Apigenin	DNMT1, DNMT3a/b, *PDX1*, *INS*, *GLUT4*	Reverses gene silencing; restores insulin signaling and glucose transport [9,11,40,42,43]..
Histone Modification	Curcumin, Resveratrol, Sulforaphane, Butyrate	HDAC3, HDAC1, SIRT1, HATs	Enhances chromatin accessibility; reactivates metabolic and anti-inflammatory genes [12,13,39,43]..
Non-coding RNA Regulation	Resveratrol, Curcumin, EGCG	miR-34a, miR-200a, miR-21, miR-126	Regulates post-transcriptional gene expression; protects against β-cell apoptosis and microvascular damage [20,21,40].
Transcription Factor Activation	Berberine, Resveratrol, EGCG, Quercetin	AMPK (via LKB1/CaMKKβ), *GLUT4*, *PEPCK*	Increases glucose uptake; inhibits hepatic gluconeogenesis and lipogenesis [6,30,41].
Antioxidant Pathway Activation	Sulforaphane, Curcumin, Berberine, Quercetin	Nrf2, *HO-1*, *SOD*, *Catalase*	Induces phase II antioxidant enzymes; mitigates oxidative stress-induced cellular damage [44–46].
Inflammatory Signaling Inhibition	Curcumin, Quercetin, Resveratrol, Omega-3 PUFAs	NF-κB, IKK complex, TNF-α, IL-6, COX-2	Suppresses pro-inflammatory cytokine production; reduces systemic low-grade inflammation [12,25,26,46]..
Nuclear Receptor Modulation	Omega-3 PUFAs (EPA/DHA), Genistein	PPAR-γ, PPAR-α, ERα/β, *PGC-1α*	Enhances fatty acid oxidation and mitochondrial biogenesis; improves insulin sensitivity [6,9,26].
Enzyme Activity Modulation	Polyphenols, Quercetin	α-glucosidase, α-amylase, PTP1B	Delays carbohydrate digestion; enhances insulin receptor signaling [6,8,25].

5. Key Bioactive Compounds and Their Anti-Diabetic Mechanisms

While the molecular mechanisms establish the theoretical framework for nutrigenomic intervention, the practical application of functional foods depends on the specific efficacy of their bioactive constituents. An overview of these key compounds, including their primary dietary sources, molecular targets, and the clinical outcomes, is provided in Table 4. This synthesis highlights the transition from "food as nutrition" to "food as a molecular regulator" of glucose homeostasis.

5.1 Resveratrol

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Resveratrol (3,5,4'-trihydroxystilbene) is a stilbene polyphenol found abundantly in grape skins, red wine, peanuts, cranberries, and Japanese knotweed, synthesized by plants in response to injury or fungal attack. Its anti-diabetic mechanisms are multifaceted and have been extensively characterized in both pre-clinical and clinical settings [8]. Resveratrol content ranges from 50 to 100 micrograms per gram in fresh grape skin and from 0.1 to 14 mg/L in red wine [6]. Resveratrol exerts primary anti-diabetic effects through: (i) SIRT1 activation, which deacetylates and activates PGC-1alpha and FOXO1, enhancing mitochondrial biogenesis and fatty acid oxidation in skeletal muscle; (ii) AMPK phosphorylation at Thr172, stimulating glucose uptake and inhibiting hepatic gluconeogenesis (Figure 3); (iii) inhibition of PDE3B, PDE8A, and PDE10A in pancreatic β-cells, leading to elevated intracellular cAMP levels and augmented glucose-stimulated insulin secretion [6]; (iv) suppression of NF-κB-mediated inflammatory cytokine production (TNF-alpha, IL-1β, IL-6), thereby reducing chronic inflammation driving insulin resistance; and (v) DNMT inhibition and SIRT1-mediated histone deacetylation, reverting aberrant methylation of metabolic genes [39]. Clinical evidence shows that resveratrol supplementation significantly lowered fasting blood glucose, HbA1c, and HOMA-IR in subjects with T2DM in randomized controlled trials. Resveratrol also stimulates GLP-1 secretion from intestinal L-cells, further amplifying insulin secretion in a glucose-dependent manner [47]. Additionally, resveratrol reduces insulin resistance through improved lipid profiles and fatty acid mobilization, with increased apoptosis of adipocytes, enhanced lipolysis, and decreased lipogenesis [48].

5.2 Curcumin

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is the principal bioactive curcuminoid derived from the rhizome of *Curcuma longa* (turmeric). Its broad-spectrum anti-diabetic activity encompasses anti-inflammatory, antioxidant, insulin-sensitising, and β-cell protective effects, mediated through multiple, interconnected molecular targets [46,49]. Curcumin modulates T2DM pathogenesis at multiple levels: (i) direct inhibition of NF-κB signalling, by suppressing IkappaB kinase (IKK) activity and preventing nuclear translocation of NF-κB, reduces expression of pro-inflammatory cytokines (IL-6, TNF-alpha, MCP-1) perpetuating insulin resistance; (ii) HDAC3 inhibition and enhanced histone acetylation at metabolic gene promoters reactivate expression of insulin, PDX-1, and GLUT4 [39]; (iii) curcumin inhibits PDE activity in pancreatic β-cells, elevating intracellular cAMP and augmenting glucose-stimulated insulin secretion [6]; (iv) protection of pancreatic islets against streptozotocin-induced oxidative stress, preserving β-cell mass and function [8,9]; and (v) Nrf2 pathway activation, inducing antioxidant enzyme expression (HO-1, SOD, catalase) and mitigating oxidative stress in diabetic complications. A landmark clinical trial demonstrated that curcumin intervention in prediabetic subjects was 100% effective in preventing progression to T2DM: none of the participants receiving curcumin developed diabetes, compared to 16.4% in the placebo group [50]. Curcumin has also demonstrated significant reductions in HbA1c, fasting blood glucose, HOMA-IR, and inflammatory markers in multiple RCTs [46,49].

5.3 Quercetin

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is one of the most abundant dietary flavonoids, found in high concentrations in onions, apples, grapes, berries, and green tea. Its anti-diabetic properties have been demonstrated across *in vitro, in vivo*, and clinical models, with mechanisms encompassing enzyme inhibition, antioxidant activity, and epigenetic regulation [6,9]. Quercetin inhibits alpha-glucosidase and alpha-amylase, slowing carbohydrate hydrolysis and reducing postprandial hyperglycemia [25]. It suppresses PTP1B, an enzyme responsible for deactivation of the insulin receptor, thereby restoring insulin signaling efficiency [6]. Regular quercetin consumption has been associated with improvement of hypertension and suppression of diabetes-induced vasoconstriction, attributable to ACE inhibition and upregulation of endothelial nitric oxide synthase (eNOS) [51]. Epigenetically, quercetin inhibits DNMTs and modulates histone methylation marks at inflammatory gene promoters, contributing to reduced NF-κB activity and improved insulin sensitivity [11].

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5.4 Genistein

Genistein (4',5,7-trihydroxyisoflavone) is the predominant isoflavone in soybeans and soy-derived products. Its structural similarity to 17β-estradiol enables binding to estrogen receptors (ERα and ERβ), but it also exerts estrogen receptor-independent effects directly relevant to T2DM management [6,9]. Genistein enhances pancreatic β-cell mass and improves insulin synthesis and secretion through upregulation of PDX-1 and Nkx6.1 transcription factors. Genistein improves glucose tolerance through enhanced GLUT4 expression in skeletal muscle and adipose tissue, partly mediated by AMPK activation [6,9]. Genistein's epigenetic activity includes methylation reversal of the insulin gene promoter, restoring insulin expression in T2DM β-cells. It also inhibits DPP-IV activity, prolonging the half-life of GLP-1 and enhancing glucose-dependent insulin secretion. Growing evidence suggests that distinct polyphenolic compounds including genistein can increase GLP-1 secretion from L-cells via direct receptor activation [6].

5.5 Berberine

Berberine is a natural plant alkaloid present in the roots and bark of *Berberis vulgaris, Coptis chinensis*, and related species [29,30,52]. It has been used for millennia in traditional Chinese and Ayurvedic medicine for the treatment of metabolic and inflammatory conditions and has emerged as one of the most pharmacologically active anti-diabetic bioactive compounds in contemporary research [29]. Berberine's anti-diabetic activity is primarily mediated through: (i) AMPK activation via LKB1 and CAMKKβ pathways, which inhibits hepatic gluconeogenesis by suppressing PEPCK and G6Pase expression, increases skeletal muscle glucose uptake via GLUT4 translocation, and promotes fatty acid oxidation; (ii) direct inhibition of mitochondrial complex I, increasing the AMP/ATP ratio and thereby activating AMPK; (iii) modulation of the insulin signaling pathway through upregulation of IRS-1 and Akt phosphorylation; (iv) epigenetic mechanisms including DNMT inhibition, histone acetylation modulation, and miRNA regulation; and (v) gut microbiota modulation, enhancing SCFA-producing bacterial populations and improving gut barrier integrity. A systematic review and meta-analysis by Xie et al. [53] demonstrated that berberine significantly reduced fasting blood glucose (FBG), 2-hour postprandial glucose, and HbA1c in RCTs of T2DM patients. A comprehensive meta-analysis published in 2025 confirmed berberine's efficacy across components of metabolic syndrome, including dyslipidemia, insulin resistance, and hypertension [29]. Berberine reduces reactive oxygen species production and increases antioxidant enzyme activity, thereby mitigating oxidative stress contributing to hyperglycemia [44].

5.6 Omega-3 Polyunsaturated Fatty Acids (PUFAs)

Omega-3 polyunsaturated fatty acids, principally eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) from marine sources, and alpha-linolenic acid (ALA, 18:3n-3) from plant sources, represent a key class of zoochemicals with well-established anti-inflammatory and metabolic regulatory properties [26]. Omega-3 PUFAs improve insulin sensitivity through: (i) AMPK activation in adipocytes and skeletal muscle, reducing lipid accumulation, ER stress, and reactive oxygen species (ROS) production [26]; (ii) PPAR-gamma and PPAR-alpha activation, increasing fatty acid oxidation and enhancing GLUT-4 receptor expression; (iii) upregulation of PGC-1alpha and NRF-1 transcription, promoting mitochondrial biogenesis; (iv) Mitofusin-2 (Mfn2) enhancement, regulating mitochondrial integrity and protecting against lipotoxicity; and (v) suppression of NLRP3 inflammasome activation, reducing IL-1β and IL-18 release [26]. At the epigenomic level, EPA and DHA modulate DNA methylation patterns in genes regulating lipid metabolism and inflammatory signaling [22].

Table 4. Summary of Key Bioactive Compounds, Gene Targets, Mechanisms, and Clinical Outcomes in T2DM Management

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Compound	Primary Food Source	Key Gene Targets	Mechanism	Clinical Outcome in T2DM
Resveratrol	Grapes (*Vitis vinifera*), red wine, peanuts	SIRT1, AMPK, PGC-1α, NF-κB	SIRT1 activation, HDAC inhibition, AMPK phosphorylation	Reduced FBG, HbA1c, and HOMA-IR; improved insulin sensitivity [6,12,48].
Curcumin	Turmeric (*Curcuma longa*)	HDAC3, NF-κB, *PDX-1*, Nrf2	HDAC inhibition, NF-κB suppression, β-cell protection	100% prevention of T2DM in prediabetes RCT; significant HbA1c reduction [39,40,46,50].
Quercetin	Onions (*Allium cepa*), apples, green tea	DNMT, PTP1B, α-glucosidase, eNOS	Enzyme inhibition, DNMT modulation, antioxidant activity	Reduced postprandial glucose, lower blood pressure, anti-inflammatory [9,11,25].
Genistein	Soybeans (*Glycine max*), soy products	*PDX-1*, *GLUT4*, DPP-IV, AMPK	β-cell mass increase, DPP-IV inhibition, AMPK activation	Improved glucose tolerance, increased insulin levels and secretion [6,9].
Berberine	*Berberis* sp., goldenseal	AMPK, *PEPCK*, *G6Pase*, IRS-1	AMPK activation, gluconeogenesis inhibition, gut microbiota modulation	Efficacy comparable to metformin; significant FBG and HbA1c reductions [28–30,53].
EGCG	Green tea (*Camellia sinensis*)	MAPK, NF-κB, DNMT1, miR-126	p38 MAPK inhibition, DNMT inhibition, SCFA production enhancement	Reduced inflammation and fasting glucose, improved insulin sensitivity [9,54,55].
Omega-3 PUFAs	Fatty fish, fish oil, flaxseed, walnuts	PPAR-γ, AMPK, PGC-1α, Mfn2	PPAR activation, AMPK activation, ER stress inhibition, mitobiogenesis	Improved insulin sensitivity, reduced TG, reduced cardiovascular risk [6,9,26].
Dietary Fibre	Oats, barley, legumes, psyllium	GPR41/43 (via SCFAs), GLP-1R, FFAR2	SCFA production, GLP-1 stimulation, glucose absorption reduction	Reduced postprandial glucose, improved HbA1c, enhanced satiety [13,14,31].

6. Gut Microbiota, Short-Chain Fatty Acids, and Nutrigenomic Interactions

The human gut microbiome is composed of trillions of microorganisms, such as bacteria, fungi, viruses and archaea, which play an important role in regulating metabolic health. The microbiome is also thought to mediate how foods are metabolized and interact with genes in T2DM [13,28]. Dysbiosis, which is the disturbance of both composition and functionality of the microbiome, has been associated with T2DM pathogenesis. This association has been documented in numerous epidemiological studies around the world. In individuals with T2DM, gut microbiota has been consistently found to lower diversity of microbial species, lower levels of bacteria that produce butyrate (especially *Faecalibacterium prausnitzii, Roseburia intestinalis*, and *Akkermansia muciniphila*), and an increase in opportunistic pathogens [13,28]. A consistent finding from studies is that the *Firmicutes-to-Bacteroidetes* ratio is altered. One key mechanism for this is that the translocation of lipopolysaccharide (LPS), which is produced by gram-negative bacteria, occurs across an impaired gut barrier, leading to the development of metabolic endotoxaemia and systemic low-grade inflammation, which then helps to maintain insulin resistance [7,28].

6.1 Short-Chain Fatty Acids (SCFAs) as Metabolic Regulators

Butyrate, acetate, and propionate (short-chain fatty acids) are produced by fermentation of dietary fiber and resistant starches in the gut by bacteria. They represent the primary mechanistic links between dietary fiber consumption and gut microbial activity, leading to improved glycemic control in T2DM [14,56]. These SCAFs are found in abundance in the gut and are produced via two separate pathways (Wood-Ljungdahl and acrylate) by bacteria such as *Roseburia, Faecalibacterium*, and *Bacteroidetes* [31]. Butyrate, produced predominantly by Firmicutes species, is the preferred energy substrate for colonocytes and exerts critical epigenomic effects through HDAC

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inhibition. Butyrate's anti-diabetic actions include: (i) stimulation of GLP-1 and PYY release from enteroendocrine L-cells via GPR41 and GPR43, enhancing glucose-dependent insulin secretion and reducing appetite; (ii) activation of PPAR Gamma in colonocytes, increasing β-oxidation and maintaining intestinal barrier integrity; (iii) induction of regulatory T cells (Tregs), suppressing obesity-associated proinflammatory macrophages; and (iv) HDAC inhibition in peripheral tissues, modulating gene expression relevant to glucose and lipid metabolism [13,28]. Evidence from Mendelian randomization analyses based on large population cohort studies supports that SCFAs are causally linked to the development of T2DM. Specifically, a host genetic determination affecting the levels of butyrate produced by the gut has been robustly associated with improved insulin levels following an oral glucose challenge ($P = 9.8x10-5$), whereas abnormalities in propionate production were found to be causally associated with an increased risk for T2DM ($P = 0.004$) [57]. These findings validate the dietary fiber-to-microbiota-to-SCFA-to-insulin signaling axis as a mechanistically sound pathway for dietary intervention.

6.2 Functional Foods as Gut Microbiota Modulators

Dietary fibres from functional foods (including β-glucans from oats and barley, inulin-type fructans from chicory and onions, pectin from fruits, and resistant starch from legumes) selectively promote the growth of beneficial SCFA-producing bacteria, functioning as prebiotics [14,58]. A randomized controlled trial with short-chain fructo-oligosaccharides (scFOS) demonstrated significant increases in Bifidobacterium and Lactobacillus populations, alongside improved metabolic markers including reduced fasting glucose and insulin resistance in prediabetic adults [58]. Polyphenols also modulate gut microbiota composition. EGCG from green tea favours the growth of SCFA-producing bacteria in human fecal samples, improving insulin sensitivity through increased production of acetate, propionate, and butyrate [6]. Resveratrol increases the relative abundance of *Akkermansia muciniphila*, a keystone species associated with improved metabolic health, reduced gut permeability, and enhanced SCFA production, in both animal models and human studies [6,28]. Berberine exerts pronounced effects on the gut microbiome, partly accounting for its anti-diabetic efficacy. Although berberine has low systemic bioavailability, its relatively high concentration in the gut allows for potential direct modulation of the microbial population by selectively inhibiting pathogenic organisms and promoting the growth of beneficial bacterial taxa as well as increasing intestinal GLP-1 secretion [29].

7. Clinical Evidence: Randomized Controlled Trials and Human Studies

To validate the efficacy of functional foods in managing T2DM, mechanistic studies from cell and animal-based studies need to be translated into clinical outcomes (Table 5). There is a growing collection of RCTs, systematic reviews, and meta-analyses that show the clinical effectiveness of bioactive compounds in regulating blood glucose levels and other associated metabolic factors.

Table 5. Key Clinical Trials of Bioactive Compounds in T2DM Management

Compound	Study Type	Population	Duration	Dose	Primary Outcome	Reference
Curcumin	RCT (double-blind)	Prediabetes (n=240)	9 months	1500 mg/day	0% vs 16.4% T2DM conversion; 100% prevention	[8]
Berberine	Systematic review & meta-analysis	T2DM patients (multiple RCTs)	12-24 weeks	900-1500 mg/day	Significant FBG, HbA1c reduction; comparable to metformin	[53]

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Resveratrol	RCT	T2DM adults	12 weeks	500-2000 mg/day	Reduced HOMA-IR, HbA1c; improved insulin sensitivity	[6]
Omega-3 PUFAs	Systematic review (35 RCTs)	T2DM and prediabetes	8-52 weeks	1-4 g/day	Reduced TG, cardiovascular disease risk; improved insulin sensitivity	[26]
scFOS (fiber)	RCT double-blind placebo-ctrl	Prediabetes adults	12 weeks	10 g/day	Increased Bifidobacterium; reduced FBG and HOMA-IR	[58]
EGCG (green tea)	RCT	Metabolic syndrome	12 weeks	500 mg/day	Reduced fasting glucose and inflammatory markers	[6]
Genistein (soy)	RCT	Postmenopausal T2DM women	6 months	54 mg/day	Improved β-cell function, reduced insulin resistance	[51]

Clinical evidence supports the effectiveness of functional food compounds with regards to diabetic management, although there are many caveats to consider. One of the primary limitations is heterogeneity (diversity) in terms of subjects, dose, duration of treatment, and methodological quality across studies that preclude direct comparisons of studies. Moreover, since curcumin, quercetin, and resveratrol have bioavailability challenges, dietary consumption of those substances is not always able to produce sufficient amounts of these compounds in tissues, therefore, it is important to create bioavailable formulations or food grade delivery systems [42,59].

There is a growing focus on using multi-omics strategies in clinical research to identify nutrigenomic biomarkers that predict unique responses to food-based interventions. Studies using precision nutrition methods, including continuous glucose monitoring, metabolomic profiling, and gut microbiome sequencing, show that the use of these personalized dietary recommendations will result in better glycemic control than the use of standardized dietary guidance [60,61].

8. Challenges, Limitations, and Future Directions

8.1 Challenges & Limitations

8.1.1 Bioavailability & Bioefficacy

One of the primary difficulties in converting the results of preclinical and animal research into valid clinical applications is the inadequate bioavailability of numerous polyphenolic compounds. Curcumin, for example, is rapidly metabolized and conjugated following ingestion, and as such, its oral bioavailability in standard formulations is estimated to be < 1% [5]. Similarly, quercetin, resveratrol, and genistein are subject to extensive first-pass metabolism, gut microbiota biotransformation, and variable absorption across individuals [49,62]. Emerging

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strategies to enhance bioavailability include encapsulation in nanoparticles, liposomes, and cyclodextrins [63–65], co-administration with piperine to inhibit metabolic conjugation [66,67], and development of phospholipid complexes [68,69]. However, the clinical evidence base for these enhanced formulations remains limited.

8.1.2 Methodological Heterogeneity in Clinical Trials

Clinical studies are characterized by a lot of methodological diversity such as varied patient populations, dosage of intervention, how long the intervention occurs, how the bioactive compounds are made, and what type of outcomes are measured. The fact that one bioactive compound can bind to many different molecular targets has major ramifications for our ability to determine the underlying cause of the clinical effects of a given compound [27,42]. Improvements in comparability, and thus evidence quality, between clinical trials can occur through the utilization of standardized methodology, and adherence to some form of reporting guidelines such as CONSORT (Consolidated Standards of Reporting Trials).

8.1.3 Individual Genetic Variation and Precision Nutrition

Individual genetic polymorphisms significantly affect the effectiveness of bioactive dietary components. For instance, genetic variations in drug metabolism enzymes (such as CYP1A2, CYP3A4 and UGT1A1) or in drug transporter molecules (including ABCG2 and SLCO1B1) and regulatory proteins that control gene transcription (such as PPAR-γ, FTO, and TCF7L2) determine the metabolism of different bioactive compounds by individuals as well as their responses [60,70]. The greatly varied results of nutrigenomic trials can be explained by genetic heterogeneity, which makes it essential to use precision nutrition methods (dietary changes can be made to account for differences in a person's genes, metabolites, or microbes) rather than general recommendations.

8.1.4 Regulatory and Ethical Considerations

The regulatory landscape for functional foods varies considerably across jurisdictions, creating challenges for evidence-based health claims and consumer trust. EFSA's strict guidelines for scientific substantiation of health claims have led to most functional foods being denied an evidence-based health claim because they did not provide adequate evidence from human intervention [10]. Several ethical concerns are raised by the commercialization of nutrigenomics testing services and personalized nutrition programs, including informed consent, data security, equity of accessibility, and possible health disparities arising if personalized nutrition is limited to wealthier segments of the population.

8.2 Future Directions

The review presents many possible future avenues of research. The most significant avenue is using artificial intelligence (AI) and machine learning together with multi-omics data to identify new interactions between diet, genes and the microbiome that would otherwise remain hidden. Additionally, researchers can use this technology to find novel phytonutrients, or compounds derived from plants, that have a biological effect. Using technologies like Brightseed's Forager, it is possible to identify new phytonutrients that help metabolize through the body. In addition, next-generation probiotics (NGPs) and symbiotic formulations, which are made up of prebiotic fiber used with distinct probiotic strains, may provide an effective method for modulating gut microbiome in T2DM. Also, clinicians could use polygenic risk scores that include information about nutrition and genetics to identify high-risk individuals who could potentially benefit from targeted diet modifications. Lastly, as mechanistic knowledge of how bioactive compounds exert their influences through epigenetics continues to expand, novel therapeutic targets for T2DM could also be discovered by the development of epigenome editing technologies.

9. Conclusion

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This review has synthesized evidence demonstrating that functional foods and their bioactive constituents represent scientifically validated, mechanistically grounded tools for the prevention and management of T2DM through nutrigenomic pathways. The convergence of nutrigenomics, epigenomics, gut microbiome science, and multi-omics technologies is reshaping our understanding of how diet interacts with the genome to modulate metabolic health. The bioactive compounds collectively engage a rich network of anti-diabetic mechanisms: epigenetic modulation through DNA methylation reversal and histone modification; transcriptional regulation of key metabolic genes; AMPK, SIRT1, NF-κB, PPAR-gamma, and PI3K/Akt pathway modulation; gut microbiota restoration and SCFA-mediated GLP-1 secretion; and direct protection of pancreatic β-cell mass and function. These mechanisms, individually and synergistically, address the core pathophysiological processes of T2DM such as insulin resistance, chronic inflammation, oxidative stress, β-cell dysfunction, and gut dysbiosis. Clinical evidence, including randomized controlled trials as well as various Meta-analysis studies, suggest that bioactive compounds are effective. Nonetheless, some barriers to implementing nutrigenomic intervention through functional foods relate to the bioavailability of these bioactive compounds, examples include heterogeneity in methodology and genetic differences among individuals. The potential for managing T2DM going forward is at the interface of precision nutrition, nutrigenomics, gut microbiome science and advanced digital technology. Through combining an individual's genomic profile, microbiome composition, metabolomic signature and dietary pattern, health professionals can develop truly personalized nutrition strategies which provide maximal glycemic relative to their risk of developing T2DM. The paradigm of 'food as medicine', grounded in rigorous molecular and clinical science, offers a compelling and sustainable complement to pharmacological approaches in the global fight against the T2DM epidemic. Continued investment in well-designed clinical trials, harmonized regulatory frameworks, and equitable access to precision nutrition technologies will be essential to realize this vision.

Declarations

Data Availability

Not applicable

Informed Consent Statement

Not applicable

Ethics Statement/Ethical Approvals

Not applicable

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Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

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Abbreviations

AMPK	Adenosine monophosphate-activated protein kinase
cAMP	Cyclic adenosine monophosphate
CONSORT	Consolidated Standards of Reporting Trials
EFSA	European Food Safety Authority
EGCG	Epigallocatechin gallate
EPA	Eicosapentaenoic acid
FBG	Fasting blood glucose
FOXO1	Forkhead box protein O1
HAT	Histone acetyltransferase
HbA1c	Glycated hemoglobin
HDAC	Histone deacetylase
HO-1	Heme oxygenase-1
HOMA-IR	Homeostatic model assessment for insulin resistance
IKK	IkappaB kinase
INS	Insulin (gene)
iNOS	Inducible nitric oxide synthase
lncRNAs	Long non-coding RNAs
LPS	Lipopolysaccharide
Mfn2	Mitofusin-2
miRNAs	MicroRNAs
mTORC1	Mammalian target of rapamycin complex 1
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGPs	Next-generation probiotics
NLRP3	NLR family pyrin domain containing 3
NRF-1	Nuclear respiratory factor 1
Nrf2	Nuclear factor erythroid 2-related factor 2
PDX-1	Pancreatic and duodenal homeobox 1
PEPCK	Phosphoenolpyruvate carboxykinase
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	Phosphoinositide 3-kinase
PPAR	Peroxisome proliferator-activated receptor
PUFAs	Polyunsaturated fatty acids
PYY	Peptide YY
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SCFAs	Short-chain fatty acids
scFOS	Short-chain fructo-oligosaccharides
SGLT2	Sodium-glucose co-transporter 2
SIRT1	Sirtuin 1
SNPs	Single nucleotide polymorphisms
T2DM	Type 2 diabetes mellitus

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