


Review Article

Integrative Molecular Therapeutics in Diabetes: The Significance of Natural Phytocompounds in Focused Treatment

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Abstract

Type 2 diabetes mellitus (T2DM) impacts more than 540 million adults worldwide, influenced by insulin resistance and β -cell dysfunction via the dysregulation of AMPK, mTOR, SIRT1, PPAR γ , GLP-1, and miRNA pathways. Existing pharmacological treatments offer symptomatic relief; however, they do not thoroughly tackle the underlying molecular mechanisms of the disease. This review consolidates recent evidence regarding phytocompounds that influence these targets, highlighting their multi-targeted therapeutic potential and enhanced safety profiles.

Significant findings indicate that gingerol (*Zingiber officinale*) promotes a 2-3-fold increase in AMPK phosphorylation and GLUT4 translocation in HepG2 cells; quercetin enhances glucose uptake by upregulating SIRT1/PPAR γ ; anthocyanins boost GLP-1 secretion; and fucoidan inhibits pathogenic miR-34a-5p, thereby restoring β -cell function. Niazirin, derived from *Moringa oleifera*, inhibits mTOR to enhance autophagy, whereas curcumin and ginsenoside Rg1 stimulate insulin signalling pathways. Studies conducted both *in vitro* and *in vivo* reveal that these compounds surpass single-target synthetics by effectively addressing hyperglycemia, inflammation, and oxidative stress simultaneously. Nanotechnology-enhanced delivery offers the potential for enhanced bioavailability. Prospects encompass precision medicine that integrates genomics, utilises AI for target identification, and modulates the microbiome to enhance personalised management of T2DM. This review article elucidates several key molecular targets in diabetes mellitus that are being addressed for the amelioration of disease severity.

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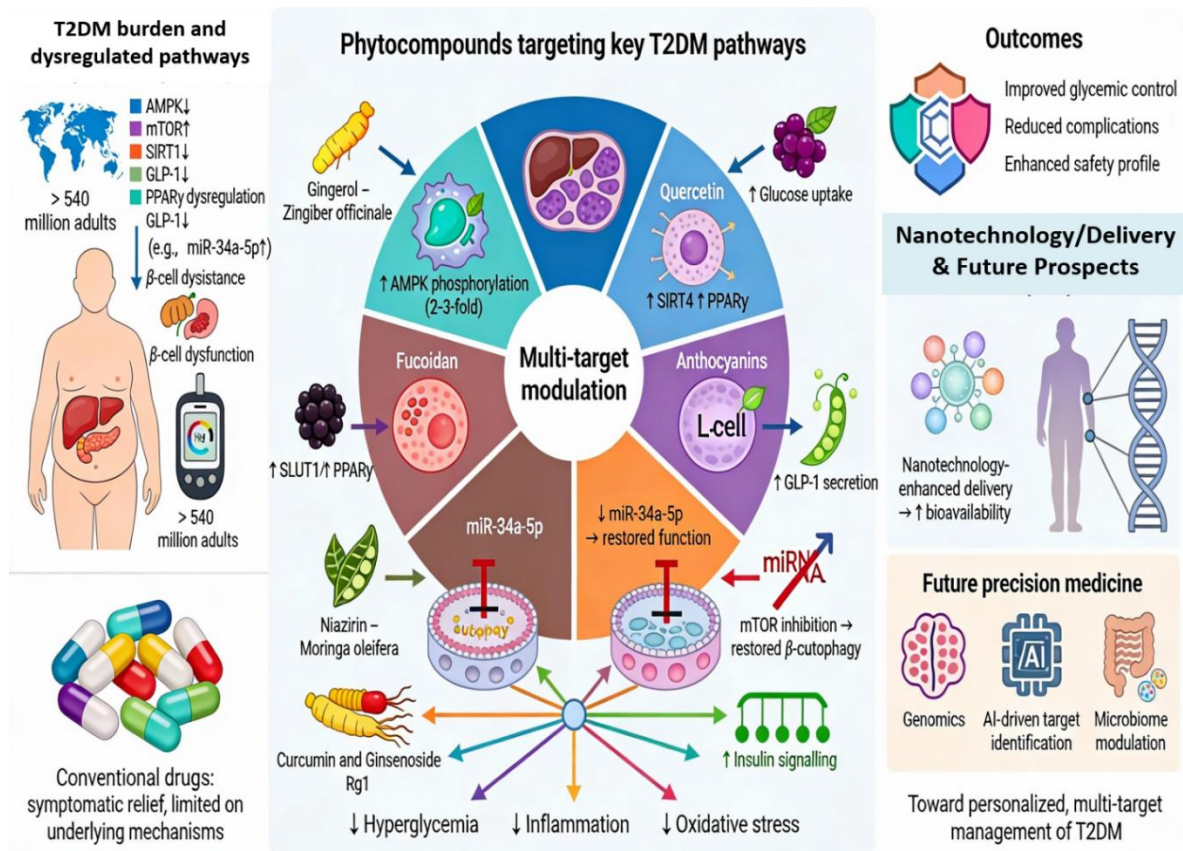
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Graphical abstract: This graphical Abstract summarises the several dysregulatory pathways associated with Type 2 Diabetes Mellitus (T2DM) and the utilisation of conventional medications, including phytochemicals derived from various plant sources, which maintain symptomatic relief and enhance glucose absorption through multi-drug modulation techniques. The prospective utilisation of a nanotechnology-based delivery system, coupled with AI-driven target identification and modification of the gut microbiota, may enhance glucose absorption, hence facilitating the personalised, multitargeted therapy of T2DM in future.

1. INTRODUCTION

Diabetes mellitus (DM), especially type 2 diabetes mellitus (T2DM), constitutes a significant global health challenge, impacting more than 540 million adults globally, with estimates suggesting that cases could surpass 783 million by 2045[1,2]. Chronic hyperglycemia, stemming from insulin resistance, impaired β-cell function, and dysregulated glucose homeostasis, defines T2DM. This condition results in significant microvascular and macrovascular complications, such as nephropathy, retinopathy, neuropathy, and cardiovascular disease[2]. Despite progress in lifestyle changes and medications aimed at enhancing insulin secretion (sulfonylureas), improving insulin sensitivity (metformin, thiazolidinediones), and modulating incretin pathways (GLP-1 receptor agonists), existing treatments mainly focus on symptom management rather than tackling the fundamental molecular mechanisms, resulting in considerable unmet therapeutic requirements[3]. Recent breakthroughs in molecular biology have shed light on crucial signalling pathways that are fundamental to the pathophysiology of T2DM. These include AMP-activated protein kinase (AMPK), mammalian target of

rapamycin (mTOR), sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor gamma (PPARγ), glucagon-like peptide-1 (GLP-1) signalling, and microRNA (miRNA)-mediated post-transcriptional regulation[4]. AMPK functions as a key metabolic regulator that promotes glucose uptake and fatty acid oxidation while inhibiting hepatic gluconeogenesis; its activation mitigates insulin resistance seen in T2DM[1]. On the other hand, the hyperactivation of mTORC1 encourages lipogenesis and leads to β-cell exhaustion, making its inhibition a potentially effective strategy [1]. The SIRT1 and PPARγ pathways play a crucial role in regulating inflammation and lipid metabolism. In contrast, dysregulated miRNAs, particularly miR-34a-5p, negatively affect β-cell survival and insulin signalling[5]. Bioactive molecules derived from medicinal plants present a valuable source of phytochemicals with the ability to target multiple pathways and demonstrate favourable safety profiles, as supported by both traditional applications and contemporary pharmacological studies [6]. Compounds such as gingerol, quercetin, curcumin, ginsenosides, and fucoidans exhibit targeted modulation of these pathways, enhancing AMPK/SIRT1 activity while

inhibiting pathogenic miRNAs and mTOR, showing greater efficacy than single-target synthetic drugs in preclinical models[7].

This review consolidates recent findings (2022-2025) on phytocompounds that influence molecular pathways related to diabetes, outlining their regulatory scope, mechanisms of action, and potential therapeutic benefits for precision medicine in the management of T2DM.

2. METHODOLOGY OF THE STUDY

A thorough literature review was performed utilising scientific databases, including PubMed, Scopus, and Web of Science, to pinpoint recent studies that concentrate on phytochemicals exhibiting antidiabetic potential. Included terms were “phytocompounds and diabetes mellitus,” “molecular targets and diabetes,” “AMPK activation natural compounds,” “miRNA modulation diabetes,” and other related phrases. Studies were chosen according to their relevance, the availability of molecular target data, and the regulatory effects evaluated either *in vitro* or *in vivo*.

3. Recent Advances in Molecular Targets for the Improvement of Diabetes Mellitus

Diabetes mellitus, particularly type-2 diabetes mellitus (T2DM), is a multifaceted metabolic condition marked by insulin resistance and dysfunction of pancreatic β -cells. Recent advances in molecular biology and pharmacology have revealed several new therapeutic targets that show potential in altering disease progression and enhancing Glycemic control. This review emphasises the latest molecular targets and therapeutic strategies centred on precision medicine approaches for managing diabetes.

3.1 AMP-activated protein kinase (AMPK) and mTOR signalling pathways

The activation of AMPK enhances insulin sensitivity and regulates glucose homeostasis through the improvement of mitochondrial function and the facilitation of glucose uptake in both skeletal muscle and liver tissues. On the other hand, blocking the mammalian target of rapamycin (mTOR) complex 1 leads to a decrease in insulin resistance and influences lipid metabolism.[6]. Strategies that enhance AMPK activity while inhibiting mTOR signalling have demonstrated positive effects on metabolic profiles in preclinical investigations. The AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signalling pathways are crucial therapeutic targets for type 2 diabetes mellitus (T2DM), focusing on insulin.

Resistance, β -cell dysfunction, and metabolic dysregulation.

Activation of AMPK promotes glucose absorption, fatty acid oxidation, and mitochondrial biogenesis, while inhibiting hepatic gluconeogenesis, hence mitigating hyperglycemia. In contrast, persistent mTORC1 hyperactivation fosters lipogenesis, β -cell depletion, and insulin resistance, rendering its targeted inhibition a promising strategy for reinstating metabolic equilibrium.[8].

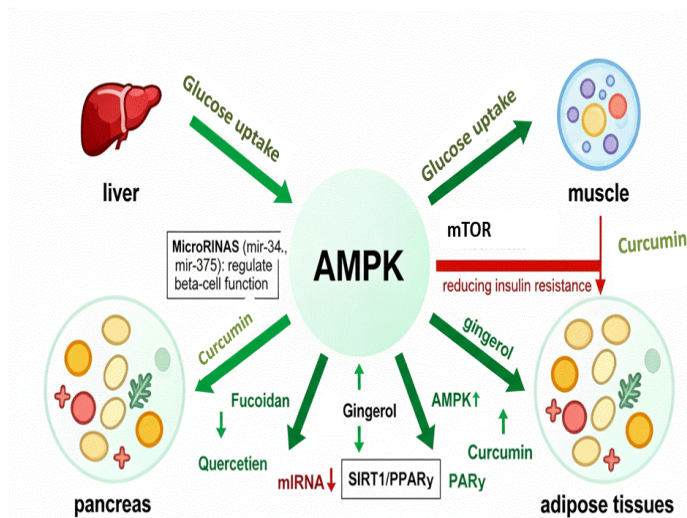
Recent advancements highlight direct and indirect AMPK activators with enhanced specificity and effectiveness (Figure 1). AdipoRon analogues, including compound X-12, stimulate AMPK through adiponectin receptors, exhibiting dose-dependent enhancements in glucose tolerance in normal mice and substantial decreases in fasting blood glucose and insulin resistance in db/db diabetic models[9]. Natural compounds such as gingerol and ginsenoside Rg1 stimulate a 2-3 fold increase in AMPK phosphorylation in HepG2 and C2C12 cells, hence promoting GLUT4 translocation and increasing insulin sensitivity.[9]. Photobiomodulation at 635 nm enhances CaMKK β expression, hence activating AMPK, whereas ligustilide increases phosphorylation in diabetic rats, highlighting non-pharmacological and herbal methodologies.[10].

Small molecule modulators, such as innovative allosteric activators, reestablish ATP homeostasis by blocking anabolic pathways, therefore designating AMPK as a viable target for pharmacological intervention in T2DM.[9]. Dapagliflozin, an SGLT2 inhibitor, promotes AMPK activation, hence inhibiting mTOR and facilitating autophagy, which reduces apoptotic cell death in diabetic mice.[6].

mTOR inhibitors demonstrate a "Janus effect": short-term administration of rapamycin deteriorates metabolism, but extended therapy improves insulin sensitivity and β -cell functionality by averting fatigue [11]. In diabetic kidney disease (DKD), rapamycin reduces albuminuria, podocyte death, and oxidative stress in high-glucose models, whereas berberine inhibits AKT/mTOR-mediated VEGF production to impede the evolution of diabetic retinopathy.[10,11]. Herbal natural mTOR inhibitors regulate signalling in the liver, pancreas, adipose tissue, and muscle, providing multi-organ advantages without the hazards associated with prolonged activation.[12]. The transition from mTORC1 to AMPK promotes β -cell development; its reverse in Type 2 Diabetes Mellitus induces dysfunction, emphasising pathway modulation as a potential therapeutic target.[13].

Dual modulation-stimulating AMPK while suppressing mTORC1-proves to be ideal, enhancing glucose homeostasis and averting problems such as diabetic nephropathy[14]. These advancements offer precise medicines that revolutionise the management of T2DM.

Figure 1: This flow diagram illustrates the role of AMPK regulation in glucose uptake and the application of curcumin, quercetin, fucoidan, and gingerol in regulating various target molecules to control the intensity of diabetes mellitus.



3.2 MicroRNAs (miRNAs)

A crucial regulator of gene expression following transcription, playing a vital role in the operation of β -cells and the signalling of insulin. Recent investigations have identified miR-690 as an agent that enhances insulin sensitivity, while miR-34a-5p has been recognised as a regulator of pancreatic endocrine dysfunction. The therapeutic antagonism of pathogenic miRNAs through the use of antagomirs is gaining recognition as an innovative strategy to enhance insulin sensitivity and promote the health of β -cells^[10]. MicroRNAs (miRNAs) are diminutive non-coding RNAs, generally 19-25 nucleotides in length, that modulate gene expression post-transcriptionally by interacting with the 3' untranslated regions (3' UTRs) of target messenger RNAs (mRNAs). These binding prompts mRNA degradation or translational inhibition, meticulously regulating protein levels essential for cellular homeostasis. In type 2 diabetes (T2D), miRNAs regulate critical pathogenic mechanisms such as insulin resistance, β -cell dysfunction, inflammation, and glucotoxicity.^[10]

3.2.1 β -cell Dysfunction and Apoptosis

In T2D β -cells, miR-34a-5p and miR-375 are elevated, inhibiting target genes such as BCL2 (anti-apoptotic) and PDX1 (β -cell development factor), resulting in compromised insulin production and heightened apoptosis. In contrast, the downregulation of miR-7 impairs the formation of insulin granules.^[10]

3.2.2 Insulin Resistance

In hepatic, adipose, and muscular tissues, members of the miR-29 family suppress IRS-1 and PTEN, hence facilitating abnormalities in insulin signalling. miR-33 targets ABCA1,

worsening dyslipidemia, whereas miR-122 overexpression stimulates hepatic gluconeogenesis via FOXO1^[15].

3.2.3 Inflammation and Oxidative Stress

miR-146a and miR-155 regulate NF- κ B signalling; their dysregulation enhances pro-inflammatory cytokines (TNF- α , IL-6) in adipose tissue macrophages, sustaining the low-grade inflammation typical of T2D [2].

3.2.4 Diagnostic and Therapeutic Capabilities

Circulating miRNAs (e.g., miR-192, miR-30d) function as non-invasive indicators for the advancement of type 2 diabetes and its consequences, such as diabetic nephropathy. Therapeutically, miRNA mimics (e.g., miR-26a to augment insulin sensitivity) and antagomirs (e.g., anti-miR-34a to protect β -cells) have potential in preclinical models, reinstating glucose homeostasis without off-target effects.^[10]

3.3 Exploring the relationship between glucagon-like peptide-1 (GLP-1) and gut microbiota

GLP-1 receptor agonists promote insulin secretion, diminish appetite, and safeguard β -cells. Recent developments in the study of gut microbiota indicate that microbial metabolites play a role in GLP-1 secretion and metabolic balance, paving the way for therapies aimed at the microbiome.^[3]

3.4 Exosomal signalling and immune modulation

Exosomes derived from natural killer cells that contain miR-1249-3p enhance insulin sensitivity by inhibiting inflammatory pathways (TLR4/NF- κ B) associated with insulin resistance. Focusing on immune cell exosomes could potentially mitigate chronic low-grade inflammation associated with diabetes.^[5]

3.5 Novel protein targets have been identified through Mendelian randomisation

Proteins, including CLSTN1, KCNJ11, MLX, and RELA, have been highlighted as promising drug targets based on genetic and proteomic research, aiding in drug development with genetic validation.^[4]

4 Innovative Therapeutic Agents and Pharmaceutical Advancement

Recent pharmacological advancements focus on these pathways, featuring AMPK activators, mTOR inhibitors, miRNA modulators, and GLP-1 receptor agonists that demonstrate enhanced efficacy and safety profiles. The diverse phytochemicals that can be utilised to modulate the levels of AMPK, GLP secretion, PPAR γ , and miR-34a-5p/miRNAs, among others, contribute to enhancing the intensity of glucose uptake and improving diabetes mellitus (Table 1). Delivery systems utilising nanotechnology improve specificity and minimise side effects associated with peptide and gene therapies. Precision medicine strategies that tailor treatments according to individual genetic and metabolic profiles are gaining prominence for effective diabetes management.^[10,16]

Table 1: This table summarises a list of various target molecules in the pathway of diabetes mellitus and the phytochemicals used to regulate glucose transporters, which in turn control the expression levels of β -cell function.

Molecular Target	Phytocompound/Source	Regulation Extent	Reference
AMPK	Gingerol (Zingiber officinale)	↑ Phosphorylation (2-3-fold in HepG2 cells); ↑ GLUT4 translocation	[10]
AMPK	Promalabaricone B	↑ Activation in L6 myotubes; improved insulin sensitivity	[7]
AMPK/SIRT1	Hawthorn acid (Crataegus spp.)	↑ AMPK/SIRT1 pathway (renal tissue, diabetic mice); ↓ oxidative stress	[17]
SIRT1/PPAR γ /AMPK	Quercetin	↑ SIRT1 expression; ↑ PPAR γ activation; improved glucose uptake	[2]
GLP-1 secretion	Anthocyanins (Ribes nigrum extract)	↑ GLP-1 levels; ↑ GLUT4 expression in T2DM models	[18]
mTOR (via AMPK)	Niazirin (Moringa oleifera)	↓ mTOR activity; ↑ autophagy in db/db mice	[18]
PPAR γ	Curcumin	↑ PPAR γ /RXR α expression; ↑ OCTN2-mediated glucose transport	[3]
miR-34a-5p/miRNAs	Fucoidan (brown algae)	↓ Pathogenic miRNA expression: restored β -cell function	[19]
AMPK	Ginsenoside Rg1 (Panax ginseng)	↑ AMPK phosphorylation; ↑ GLUT4 in C2C12 cells	[18]
Insulin signalling	Atractylenolide II	↑ IRS-1 tyrosine phosphorylation; direct insulin cascade restoration	[10]

5. Exploring Future Directions Research

The advancement of diabetes mellitus management is rooted in a comprehensive strategy that combines molecular biology, genomics, and tailored medical approaches. New molecular targets like AMPK, mTOR, miRNAs, GLP-1 signalling, and immune exosomes signify the initial steps toward a more comprehensive therapeutic landscape tailored to individual patient profiles. Recent developments in high-throughput sequencing, single-cell omics, and artificial intelligence will facilitate the discovery of new targets and biomarker-driven patient stratification, ultimately enhancing treatment precision and effectiveness.[16].

The integration of nanotechnology and sophisticated drug delivery systems is set to transform the administration of peptide-based drugs, gene therapies, and RNA-based modulators, reducing systemic side effects and improving target specificity. Combination therapies that concurrently influence various molecular pathways present opportunities for synergistic effects, tackling the diversity in diabetes pathophysiology[10].

Interventions centred on the microbiome, utilising probiotics, prebiotics, and microbial metabolite mimetics, present a compelling opportunity to influence endogenous GLP-1 secretion and inflammation, thereby enhancing existing treatment strategies. Additionally, targeting chronic low-grade inflammation through immune modulation holds potential for restoring insulin sensitivity and preventing complications related to diabetes[3,5].

The incorporation of real-world data alongside longitudinal cohort studies will expedite the validation of these innovative targets and facilitate the movement from laboratory research to clinical application, thereby broadening the range of safe and effective treatment options. Ultimately, these advancements

Hold the potential to change diabetes into a manageable condition, offering personalised long-term disease control and minimising the burden of complications.

CONCLUSION

MicroRNAs play a crucial role as post-transcriptional regulators that connect genetic predisposition, environmental influences, and metabolic stress in the development of type 2 diabetes mellitus. Dysregulated miRNA networks play a crucial role in the onset and progression of disease, as well as in chronic complications, by coordinately modulating β -cell survival, insulin secretion, insulin signalling, lipid metabolism, and inflammatory pathways. Their presence in circulation, stability in body fluids, and tissue-specific expression patterns render them promising candidates for biomarkers aimed at early diagnosis, risk stratification, and monitoring therapeutic responses in T2D. The experimental modulation of pathogenic miRNAs through the use of mimics and antagomirs has shown significant results, including the restoration of insulin sensitivity, preservation of β -cell mass, and reduction of inflammation and oxidative stress in preclinical models. These findings underscore their potential as innovative molecular therapeutics for future applications. Nonetheless, obstacles persist concerning delivery mechanisms, unintended effects, prolonged safety, and differences among individuals. Combining miRNA profiling with genomics, metabolomics, and clinical phenotyping could facilitate personalised, mechanism-driven interventions that advance beyond mere symptomatic Glycemic control to achieve genuine disease modification in type 2 diabetes.

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