DOI: 10.66069/ojspub.27450747

Natural Monomers Targeting the AMPK/GLP-1 Signaling Axis in the Treatment of Type 2 Diabetes: Molecular Mechanisms and Translational Prospects

Jiake Wang[1], Yu Wang[1], Ao Yang[1], Yuqi Niu[1], Songyi Wang, Ye Lei[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]The Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

Abstract: ***Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease characterized by insulin resistance, beta-cell dysfunction, ectopic lipid accumulation, chronic low-grade inflammation, and multi-organ metabolic inflexibility. Although modern pharmacotherapy has greatly improved glycemic control, the durability of treatment responses remains constrained by disease heterogeneity, incomplete tissue coverage, adverse effects, and limited access in many settings. AMP-activated protein kinase (AMPK) and glucagon-like peptide-1 (GLP-1) signaling are two of the most validated metabolic axes in diabetes therapeutics. AMPK functions as a master energy sensor that suppresses hepatic gluconeogenesis, enhances skeletal muscle glucose uptake, promotes fatty acid oxidation, improves mitochondrial quality control, and dampens inflammation. GLP-1 regulates glucose-dependent insulin secretion, glucagon suppression, gastric emptying, appetite, and beta-cell survival, while also exerting extra-pancreatic actions in the liver, kidney, cardiovascular system, and central nervous system. Increasing evidence indicates that these pathways are not isolated. Instead, they intersect at the levels of intestinal L-cell biology, autophagy, mitochondrial homeostasis, inflammation, and tissue-specific insulin sensitivity, forming an integrated AMPK/GLP-1 signaling axis with substantial relevance to T2DM. Natural monomers have emerged as attractive modulators of this axis because they often act on multiple targets simultaneously, including intestinal nutrient sensing, DPP-4 activity, gut microbiota-derived incretin regulation, AMPK phosphorylation, oxidative stress, and inflammatory cascades. Representative compounds such as berberine, resveratrol, curcumin, quercetin, genistein, chlorogenic acid, epigallocatechin gallate (EGCG), naringenin, ginsenosides, and baicalin have shown anti-diabetic activity in cellular systems, animal models, and selected human studies. However, the literature remains fragmented, with many compounds being studied either as generic "anti-diabetic phytochemicals" or as isolated AMPK activators without sufficient attention to their mechanistic convergence with GLP-1 biology. This review synthesizes current evidence on the molecular crosstalk between AMPK and GLP-1 signaling and evaluates how natural monomers engage this axis across the gut-pancreas-liver-muscle-adipose network. We summarize representative compounds, compare their organ-level mechanisms, discuss pharmacokinetic and translational barriers, and outline priorities for future drug development. We argue that the AMPK/GLP-1 axis provides a useful conceptual framework for reclassifying natural monomers from single-pathway agents into network modulators with potential value as adjuncts, sensitizers, or leads for next-generation multi-target anti-diabetic therapies.***

Keywords: Type 2 diabetes mellitus, AMP-activated protein kinase, Glucagon-like peptide-1, Natural monomers, Phytochemicals, Insulin resistance, Beta-cell protection, Gut-liver axis.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease characterized by insulin resistance, beta-cell dysfunction, ectopic lipid accumulation, chronic low-grade inflammation, and multi-organ metabolic inflexibility [1]. The pathobiology of T2DM extends beyond hyperglycemia and involves hepatic overproduction of glucose, impaired skeletal muscle glucose disposal, dysfunctional adipose tissue lipolysis, enteroendocrine abnormalities, mitochondrial stress, and progressive beta-cell exhaustion [1-5].

Among validated therapeutic nodes, AMP-activated protein kinase (AMPK) and glucagon-like peptide-1 (GLP-1) are especially important [6]. AMPK is a master energy sensor that shifts metabolism away from ATP-consuming anabolic programs and toward ATP-generating catabolic pathways [7, 8]. GLP-1 is an incretin hormone that enhances glucose-dependent insulin secretion, suppresses glucagon, slows gastric emptying, reduces food intake, and protects beta cells [9]. The striking clinical success of GLP-1 receptor agonists and dual incretin therapeutics highlights the therapeutic importance of this pathway, while decades of mechanistic work continue to support AMPK as a core disease-modifying target in T2DM [10].

A growing body of work suggests that AMPK and GLP-1 should not be considered independent modules. Intestinal nutrient sensing, L-cell secretion, autophagy, mitochondrial quality control, inflammation, and tissue-specific insulin sensitivity all create points of intersection between the two pathways [7, 11]. This integrated view is especially useful for natural product pharmacology because most natural monomers are pleiotropic regulators rather than highly selective single-receptor ligands. The AMPK/GLP-1 axis therefore offers a mechanistically coherent framework for reorganizing the literature on anti-diabetic phytochemicals.

2. Biological Basis of the AMPK/GLP-1 Signaling Axis

T2DM is a complex metabolic disorder characterized by progressive insulin resistance, pancreatic β-cell dysfunction, chronic low-grade inflammation, and dysregulated glucose and lipid metabolism [1]. Although current pharmacological strategies targeting insulin secretion, insulin sensitivity, and incretin signaling have substantially improved glycemic management, the progressive nature of T2DM highlights the need for therapeutic approaches capable of restoring metabolic homeostasis rather than simply controlling blood glucose levels [2]. In this context, the AMP-activated protein

kinase (AMPK)/glucagon-like peptide-1 (GLP-1) signaling axis has emerged as a critical regulatory network integrating energy sensing, endocrine communication, and multi-organ metabolic adaptation [6, 10]. Increasing evidence indicates that natural monomers derived from medicinal plants can regulate this axis through diverse molecular mechanisms, providing new perspectives for metabolic disease intervention.

AMPK is a highly conserved serine/threonine kinase that functions as a master regulator of cellular energy balance [6]. The AMPK complex consists of a catalytic α-subunit and regulatory β- and γ-subunits, allowing the enzyme to respond to alterations in intracellular energy status [12]. Under conditions of metabolic stress, including reduced ATP availability and increased AMP/ADP levels, AMPK is activated to restore energy equilibrium by stimulating ATP-generating pathways while suppressing ATP-consuming anabolic processes [13]. The activation of AMPK is primarily mediated by upstream kinases, particularly liver kinase B1 (LKB1), which phosphorylates the critical activation site Thr172 on the AMPK α-subunit. In addition, calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ) activates AMPK in response to intracellular calcium fluctuations, suggesting that AMPK integrates both energy and calcium-dependent signals [14, 15]. Other regulatory factors, including SIRT1, adiponectin signaling, reactive oxygen species (ROS), and mitochondrial stress responses, further contribute to AMPK regulation under physiological and pathological conditions [16].

In T2DM, impaired AMPK activity contributes to widespread metabolic disturbances. In the liver, reduced AMPK signaling promotes excessive gluconeogenesis and lipid synthesis, resulting in fasting hyperglycemia and hepatic steatosis [17]. AMPK activation suppresses hepatic glucose production through inhibition of key gluconeogenic transcriptional programs, including the FOXO1 and PGC-1α pathways, thereby reducing the expression of rate-limiting enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). Meanwhile, AMPK inhibits de novo lipogenesis by suppressing sterol regulatory element-binding protein-1c (SREBP-1c) activity and phosphorylating acetyl-CoA carboxylase (ACC), leading to enhanced fatty acid oxidation and improved lipid homeostasis [18, 19]. Therefore, hepatic AMPK activation represents an important mechanism for reversing metabolic abnormalities associated with insulin resistance.

In skeletal muscle, AMPK promotes glucose utilization by enhancing glucose transporter 4 (GLUT4) translocation to the plasma membrane and increasing glucose uptake independently of insulin signaling [20]. Furthermore, AMPK stimulates mitochondrial biogenesis and oxidative metabolism through regulation of PGC-1α, thereby improving energy efficiency and reducing metabolic stress [7, 21, 22]. In adipose tissue, AMPK activation suppresses excessive lipolysis, decreases inflammatory adipokine production, and contributes to improved systemic insulin sensitivity [23, 24]. These diverse actions demonstrate that AMPK functions as a metabolic coordinator rather than a simple glucose-regulating molecule [25]. Consequently, pharmacological activation of AMPK is increasingly considered a strategy for metabolic reprogramming that simultaneously influences glucose metabolism, lipid metabolism, mitochondrial function, and inflammatory homeostasis.

GLP-1 is an incretin hormone primarily produced by enteroendocrine L cells located in the distal intestine [25]. Following nutrient ingestion, including exposure to glucose, fatty acids, and amino acids, intestinal L cells release GLP-1 into the circulation [26]. However, endogenous GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), resulting in a short biological half-life [27]. The physiological actions of GLP-1 are mainly mediated through the GLP-1 receptor (GLP-1R), a G protein-coupled receptor expressed in pancreatic β cells and various extra-pancreatic tissues [28]. Upon GLP-1R activation, intracellular cyclic adenosine monophosphate (cAMP) production is increased through adenylate cyclase activation, followed by stimulation of protein kinase A (PKA) and exchange protein directly activated by cAMP 2 (Epac2) [29, 30]. These signaling cascades enhance glucose-dependent insulin secretion, promote β-cell function, and suppress inappropriate glucagon release, collectively contributing to improved glycemic control [31].

Beyond its classical incretin function, GLP-1 has increasingly been recognized as a systemic metabolic regulator [8]. In pancreatic β cells, GLP-1 signaling enhances insulin biosynthesis, promotes cell survival, and protects against glucolipotoxicity-induced apoptosis by reducing oxidative stress and endoplasmic reticulum stress [11, 32, 33]. In the liver, GLP-1-related pathways improve insulin sensitivity and lipid metabolism through regulation of inflammation, mitochondrial function, and autophagic processes [30, 34]. Although hepatocytes generally exhibit limited direct GLP-1R expression compared with pancreatic tissue, hepatic metabolic improvement induced by GLP-1-based therapies is considered to involve indirect endocrine communication, neural pathways, and modulation of systemic metabolic states [34]. In cardiovascular and renal systems, GLP-1 signaling contributes to endothelial protection, oxidative stress reduction, and attenuation of inflammatory injury, supporting the broader organ-protective properties of GLP-1-based interventions [34, 35].

Importantly, AMPK and GLP-1 signaling are not isolated pathways but form an interconnected regulatory network involved in metabolic adaptation [8]. Several studies suggest that GLP-1 signaling can influence AMPK activity through modulation of intracellular energy metabolism, mitochondrial function, and calcium-dependent signaling. Conversely, AMPK activation may enhance incretin responsiveness by improving cellular metabolic flexibility and reducing metabolic stress [10, 20]. This reciprocal interaction provides a mechanistic basis for understanding how natural monomers can exert coordinated effects on glucose metabolism through simultaneous regulation of energy sensing and endocrine signaling [36].

The interaction between AMPK and GLP-1 is particularly relevant in the context of multi-organ metabolic regulation. In the intestine, nutrient sensing, gut microbiota-derived metabolites, bile acid signaling, and epithelial metabolic status influence GLP-1 secretion, while AMPK contributes to

maintaining intestinal energy balance and barrier function [37, 38]. In pancreatic islets, GLP-1 supports insulin secretion and β-cell survival, whereas AMPK maintains mitochondrial quality control and cellular stress adaptation [39]. In peripheral tissues, including liver, skeletal muscle, and adipose tissue, AMPK and GLP-1-associated signaling pathways converge on common biological processes such as mitochondrial homeostasis, lipid metabolism, autophagy, and inflammation control [40, 41]. Therefore, targeting the AMPK/GLP-1 axis represents a therapeutic concept that extends beyond conventional glucose lowering and focuses on restoring metabolic equilibrium across multiple organs.

3. Representative Natural Monomers Targeting the AMPK/GLP-1 Axis

Berberine remains the strongest prototype for axis-based analysis. It activates AMPK across the liver, skeletal muscle, and adipose tissue; suppresses hepatic gluconeogenesis; improves glucose uptake; and reduces lipid accumulation [42]. Just as importantly, berberine can increase endogenous GLP-1 tone through direct stimulation of L-cell secretion, bitter taste receptor signaling, DPP-4-related mechanisms, microbiota remodeling, and protection of intestinal enterocytes from metabolic stress [43, 44]. This breadth makes berberine one of the clearest examples of a natural monomer that engages both the AMPK and incretin arms of T2DM pathophysiology [45, 46].

Resveratrol and curcumin are often described broadly as antioxidant polyphenols, but this label understates their metabolic specificity [47]. Resveratrol repeatedly activates AMPK-associated pathways, improves insulin sensitivity, enhances mitochondrial function, and attenuates inflammatory stress [48, 49].

Curcumin influences AMPK-linked lipid and inflammatory control while also improving intestinal integrity and beta-cell stress resistance [50, 51]. Direct GLP-1 secretagogue evidence is not as robust as for berberine, yet both compounds fit the AMPK/GLP-1 framework as indirect axis stabilizers that improve the intestinal and metabolic terrain required for effective incretin action [51-56].

Ginsenosides are major bioactive saponins derived from Panax species and represent important natural compounds with diverse pharmacological activities [57]. Increasing evidence suggests that ginsenosides exert beneficial effects against metabolic disorders through regulation of AMPK signaling, mitochondrial function, glucose metabolism, and inflammatory responses [58]. Among various ginsenosides, Rg1, Rb1, and compound K have been extensively investigated for their roles in improving insulin sensitivity and metabolic homeostasis [59]. Furthermore, emerging studies indicate that ginsenosides may regulate incretin-associated pathways through modulation of intestinal microbiota and enhancement of GLP-1 secretion, highlighting their potential as multifunctional metabolic regulators [60].

Quercetin, genistein, chlorogenic acid, EGCG, naringenin, ginsenosides, and baicalin extend this concep. Quercetin is a naturally occurring flavonoid widely distributed in fruits, vegetables, and medicinal plants [61]. Quercetin improves glucose uptake and AMPK activation in muscle and other tissues and may also support gut barrier restoration [62-65]. Genistein combines insulin-sensitizing, mitochondrial, and gut microbiota-related actions. Chlorogenic acid and EGCG are food-derived phenolics with meaningful effects on AMPK-centered glucose and lipid regulation [66-70]. Naringenin can improve glucose uptake and AMPK phosphorylation and may also intersect with DPP-4-related biology in combination systems. Collectively, these compounds argue for a systems-level, not receptor-centric, interpretation of natural anti-diabetic pharmacology. Representative natural monomers that regulate the AMPK/ GLP-1 signaling axis, their target organs, molecular mechanisms, and translational characteristics are summarized in Table 1.

Table 1: Representative natural monomers targeting the AMPK/GLP-1 axis in T2DM.

Monomer	Chemical class	Main organs	Key AMPK/GLP-1-related mechanisms	Evidence level	Translational note
Berberine	Isoquinoline alkaloid	Liver, gut, islets	AMPK activation; hepatic gluconeogenesis ↓; intestinal GLP-1 secretion ↑; DPP-4 / microbiota modulation	Cell, rodent, limited human	Best-developed axis prototype; poor oral bioavailability remains a major barrier
Resveratrol	Stilbene polyphenol	Liver, muscle, adipose	AMPK/SIRT1 activation; oxidative stress ↓; insulin sensitivity ↑; indirect incretin support	Cell, rodent, small clinical trials	Effect sizes depend strongly on formulation and dose
Curcumin	Diarylheptanoid polyphenol	Gut, liver, islets	AMPK-linked inflammatory control; barrier repair; lipotoxic stress ↓; possible incretin-supportive microenvironment	Rodent, meta-analyses of small clinical trials	Requires formulation engineering for consistent exposure
Quercetin	Flavonol	Muscle, gut, vasculature	AMPK activation; glucose uptake ↑; intestinal barrier restoration; inflammation ↓	Cell, rodent, limited human	Strong mechanistic rationale, but clinical standardization is limited
Genistein	Isoflavone	Muscle, liver, gut	Insulin sensitivity ↑; mitochondrial support; gut microbiota interactions; possible indirect GLP-1 support	Rodent and selected human metabolic studies	May be phenotype-dependent and microbiota-sensitive
Chlorogenic acid	Phenolic acid	Gut, liver, adipose	AMPK-related glucose/lipid regulation; adiponectin signaling; glucose tolerance ↑	Rodent and nutritional evidence	Useful as a food-derived low-intensity modulator
EGCG	Catechin	Liver, gut, beta cells	AMPK activation; gluconeogenesis ↓; oxidative stress ↓; gut-metabolic signaling support	Cell, rodent, selected human studies	Exposure and tolerability must be considered at high doses
Naringenin	Flavanone	Muscle, liver	Glucose uptake ↑; AMPK phosphorylation ↑; possible DPP-4-related synergy	Cell and rodent	Likely better suited to combination strategies
Ginsenosides	Triterpenoid saponins	Liver, adipose, gut	AMPK activation; steatosis ↓; inflammation ↓; host-microbiota interactions	Extensive preclinical and some clinical support for ginseng products	Subtype-specific effects need clarification
Baicalin	Flavone glycoside	Liver, kidney, heart	AMPK-linked antioxidant, anti-inflammatory, and anti-fibrotic actions	Predominantly rodent	Most evidence concerns complications rather than primary glycemic endpoints

4. Organ-level Mechanisms Across the AMPK/ GLP-1 Network

The intestine is the most logical entry point because endogenous GLP-1 is generated there and many monomers have extensive luminal exposure despite limited systemic bioavailability [11]. Natural monomers can enhance incretin biology by stimulating L-cell secretion, attenuating DPP-4 activity, improving intestinal barrier integrity, and remodeling microbiota-derived signals [11]. Berberine provides the clearest evidence, while several flavonoids and polyphenols may work more indirectly by suppressing mucosal inflammation and restoring the endocrine quality of nutrient sensing [39].

At the level of pancreatic beta cells, the AMPK/GLP-1 axis addresses two major pathogenic processes: insufficient trophic signaling and excessive glucolipotoxic stress [29]. Natural monomers may enhance endogenous GLP-1 tone, restore GLP-1 receptor signaling, or activate AMPK-linked mechanisms that improve mitochondrial quality control, autophagy, and apoptosis resistance [71]. This dual logic is particularly attractive in early T2DM or prediabetes, where preserving residual beta-cell function may alter the long-term trajectory of disease.

The liver remains one of the most reproducible targets of AMPK-activating monomers. Berberine, resveratrol, curcumin, chlorogenic acid, ginsenosides, and baicalin all show varying ability to suppress gluconeogenesis, restrain lipogenesis, and reduce steatosis [72]. GLP-1-related mechanisms also intersect with hepatic autophagy and lipid handling through AMPK/mTOR-linked pathways [73]. Thus, hepatic effects within this axis should be interpreted not simply as fasting glucose control, but as relief of lipotoxic organ stress that propagates systemic insulin resistance.

Skeletal muscle and adipose tissue are equally important because they determine systemic insulin sensitivity and postprandial nutrient handling [13]. Quercetin, resveratrol, genistein, and naringenin-related compounds improve muscle glucose uptake and AMPK responsiveness, whereas AMPK activity in adipose tissue constrains maladaptive lipolysis and inflammatory signaling [13]. Even when a natural monomer does not clearly stimulate GLP-1 release, improved peripheral AMPK responsiveness can amplify the systemic benefit of endogenous incretin signaling by reducing insulin demand and ectopic lipid flux [21].

Kidney, vascular, and other complication-related tissues also respond to this axis [74]. GLP-1-centered interventions can improve autophagy and organ protection through AMPK/mTOR-related mechanisms, while natural monomers such as quercetin, baicalin, resveratrol, and EGCG show renoprotective, vasculoprotective, and anti-inflammatory actions in diabetic models. Although such studies should not be overinterpreted as proof of primary glucose-lowering efficacy, they support the idea that axis-targeting compounds may exert systems-level benefit beyond glycemia alone.

5. Translational opportunities and limitations

The major translational opportunity for natural monomers lies not in replacing established anti-diabetic medications, but in their potential role as metabolic modulators that reshape disease-associated metabolic environments. Rather than acting as single-target glucose-lowering agents, natural monomers may provide complementary benefits by improving insulin sensitivity, restoring metabolic flexibility, regulating intestinal endocrine signaling, and enhancing responsiveness to existing therapies. Within this framework, the AMPK/GLP-1 axis provides a mechanistically accessible platform for evaluating therapeutic activity, with measurable biomarkers including AMPK phosphorylation, GLP-1 secretion dynamics, DPP-4 activity, autophagy-related markers, microbiota-derived metabolites, and tissue-specific indicators of insulin sensitivity and steatosis. The major regulatory nodes within the AMPK/GLP-1 axis, corresponding candidate monomers, measurable biomarkers, and translational challenges are summarized in Table 2.

Table 2: Functional nodes within the AMPK/GLP-1 signaling axis and their translational implications for natural monomer-based therapy in T2DM

Axis node	Representative monomers	Useful biomarkers/readouts	Opportunity	Current limitation
Intestinal L-cell secretion	Berberine; selected polyphenols	Fasting/postprandial GLP-1, L-cell markers, TAS2R/PLC signaling	Direct enhancement of endogenous incretin tone	Usually indirect, model-dependent, and difficult to separate from microbiota effects
DPP-4 restraint	Berberine, flavonoids (e.g., naringenin)	DPP-4 activity, active GLP-1 half-life	May prolong native GLP-1 action without exogenous peptide therapy	Potency is generally weaker than dedicated DPP-4 inhibitors
AMPK activation	Berberine, resveratrol, quercetin, genistein, EGCG, ginsenosides	p-AMPK, ACC phosphorylation, GLUT4 translocation, hepatic PEPCK and G6Pase expression	Broad metabolic remodeling across liver, muscle, and adipose tissue	Tissue specificity and exposure-response relationships remain underdefined
Autophagy / mitophagy	Berberine, baicalin, ginsenosides	LC3-II, Beclin-1, p62, mTOR activity, mitochondrial stress markers	Useful in lipotoxic liver, kidney, and beta-cell stress	Assays are heterogeneous and often overinterpreted
Microbiota-dependent signaling	Berberine, genistein, chlorogenic acid, ginsenosides	SCFAs, bile acids, microbiome composition, intestinal barrier markers	Can amplify gut-restricted compounds despite low bioavailability	Causality is hard to prove without transplantation or depletion experiments
Clinical translation	Representative monomers	HbA1c, FBG, HOMA-IR, body weight, liver fat, mechanistic biomarkers	Potential value as adjuncts, sensitizers, or lead compounds	Few biomarker-rich, adequately powered randomized trials

Despite promising biological activity, several limitations currently restrict clinical translation. Most available evidence is derived from cellular and animal models with heterogeneous dosing regimens and inconsistent endpoint selection. Furthermore, poor oral bioavailability, incomplete characterization of active metabolites, and insufficient discrimination between direct pharmacological effects and microbiota-mediated actions remain major challenges. Clinical studies are often limited by small sample sizes and lack of mechanistic biomarkers, resulting in difficulty in establishing exposure-response relationships and causal mechanisms.

Future studies should therefore prioritize mechanism-driven compound selection, standardized exposure assessment, and biomarker-guided clinical evaluation. Particular attention should be given to gut-centered pharmacology, including intestinal GLP-1 secretion, DPP-4 activity, bile acid signaling, and microbiota-derived metabolites, especially for compounds with limited systemic exposure but strong metabolic effects.

Combination strategies with established therapies, including metformin, GLP-1 receptor agonists, and DPP-4 inhibitors, represent another promising direction. In parallel, advances in formulation technologies, such as nanoformulations, prodrugs, tissue-targeted delivery systems, and gut-retentive approaches, may overcome pharmacokinetic limitations.

Ultimately, precision phytopharmacology based on metabolic phenotype stratification may enable identification of patient populations most likely to benefit from specific natural monomers, including individuals characterized by obesity-associated insulin resistance, hepatic steatosis, microbiota dysbiosis, or early β-cell dysfunction.

6. Conclusion

The AMPK/GLP-1 signaling axis provides a powerful framework for understanding how natural monomers exert anti-diabetic effects across multiple organs and molecular layers. Rather than functioning merely as generic antioxidants or loosely defined herbal hypoglycemic agents, many natural monomers act as distributed metabolic modulators regulating intestinal incretin biology, cellular energy sensing, mitochondrial function, autophagy, inflammation, and tissue insulin sensitivity.

Berberine currently represents the most comprehensive example of AMPK/GLP-1 axis modulation, while resveratrol, curcumin, quercetin, genistein, chlorogenic acid, EGCG, naringenin, ginsenosides, and baicalin provide additional mechanistic evidence through distinct but partially overlapping pathways. However, successful clinical translation requires moving beyond general claims of anti-diabetic activity toward exposure-aware, biomarker-guided, and mechanism-based evaluation. Natural monomers may therefore be best positioned as adjunctive metabolic modulators or therapeutic lead structures rather than direct replacements for established AMPK- or incretin-based therapies.

References

[1] DONATH M Y, SHOELSON S E. Type 2 diabetes as an inflammatory disease [J]. Nat Rev Immunol, 2011, 11(2): 98-107.

[2] DEFRONZO R A, FERRANNINI E, GROOP L, et al. Type 2 diabetes mellitus [J]. Nat Rev Dis Primers, 2015, 1: 15019.

[3] KAHN S E, COOPER M E, DEL PRATO S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future [J]. Lancet, 2014, 383(9922): 1068-1083.

[4] KORNBERG K. You, Me, and We: Biolabs for the 21st Century [J]. Cell, 2016, 164(6): 1097-1100.

[5] DAVIES M J, ARODA V R, COLLINS B S, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [J]. Diabetes Care, 2022, 45(11): 2753-2786.

[6] HARDIE D G, ROSS F A, HAWLEY S A. AMPK: a nutrient and energy sensor that maintains energy homeostasis [J]. Nat Rev Mol Cell Biol, 2012, 13(4): 251-262.

[7] HERZIG S, SHAW R J. AMPK: guardian of metabolism and mitochondrial homeostasis [J]. Nat Rev Mol Cell Biol, 2018, 19(2): 121-135.

[8] MüLLER T D, FINAN B, BLOOM S R, et al. Glucagon-like peptide 1 (GLP-1) [J]. Mol Metab, 2019, 30: 72-130.

[9] DRUCKER D J. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1 [J]. Cell Metab, 2018, 27(4): 740-756.

[10] NAUCK M A, QUAST D R, WEFERS J, MEIER J J. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art [J]. Mol Metab, 2021, 46: 101102.

[11] DRUCKER D J. The biology of incretin hormones [J]. Cell Metab, 2006, 3(3): 153-165.

[12] CARLING D. AMPK signalling in health and disease [J]. Curr Opin Cell Biol, 2017, 45: 31-37.

[13] HARDIE D G. AMP-activated protein kinase: maintaining energy homeostasis at the cellular and whole-body levels [J]. Annu Rev Nutr, 2014, 34: 31-55.

[14] PETERSON G, REZNIKOFF W. Tn5 transposase active site mutations suggest position of donor backbone DNA in synaptic complex [J]. J Biol Chem, 2003, 278(3): 1904-1909.

[15] HAWLEY S A, PAN D A, MUSTARD K J, et al. Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase [J]. Cell Metab, 2005, 2(1): 9-19.

[16] RUDERMAN N B, XU X J, NELSON L, et al. AMPK and SIRT1: a long-standing partnership? [J]. Am J Physiol Endocrinol Metab, 2010, 298(4): E751-760.

[17] LEE B C, KIM M S, PAE M, et al. Adipose Natural Killer Cells Regulate Adipose Tissue Macrophages to Promote Insulin Resistance in Obesity [J]. Cell Metab, 2016, 23(4): 685-698.

[18] OAKHILL J S, SCOTT J W, KEMP B E. Structure and function of AMP-activated protein kinase [J]. Acta Physiol (Oxf), 2009, 196(1): 3-14.

[19] VILELA M, DANUSER G. What's wrong with correlative experiments? [J]. Nat Cell Biol, 2011, 13(9): 1011.
[20] RICHTER E A, RUDERMAN N B. AMPK and the biochemistry of exercise: implications for human health and disease [J]. Biochem J, 2009, 418(2): 261-275.
[21] JäGER S, HANDSCHIN C, ST-PIERRE J, SPIEGELMAN B M. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha [J]. Proc Natl Acad Sci U S A, 2007, 104(29): 12017-12022.
[22] ECK M J, MANLEY P W. The interplay of structural information and functional studies in kinase drug design: insights from BCR-Abl [J]. Curr Opin Cell Biol, 2009, 21(2): 288-295.
[23] AROMATARIS E C, ROBERTS M L, BARRITT G J, RYCHKOV G Y. Glucagon activates Ca2+ and Cl- channels in rat hepatocytes [J]. J Physiol, 2006, 573(Pt 3): 611-625.
[24] LIM C T, KOLA B, KORBONITS M. AMPK as a mediator of hormonal signalling [J]. J Mol Endocrinol, 2010, 44(2): 87-97.
[25] HARDIE D G. AMPK: positive and negative regulation, and its role in whole-body energy homeostasis [J]. Curr Opin Cell Biol, 2015, 33: 1-7.
[26] GRIBBLE F M, REIMANN F. Enteroendocrine Cells: Chemosensors in the Intestinal Epithelium [J]. Annu Rev Physiol, 2016, 78: 277-299.
[27] DEACON C F. What do we know about the secretion and degradation of incretin hormones? [J]. Regul Pept, 2005, 128(2): 117-124.
[28] DRUCKER D J, NAUCK M A. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes [J]. Lancet, 2006, 368(9548): 1696-1705.
[29] HOLST J J. The physiology of glucagon-like peptide 1 [J]. Physiol Rev, 2007, 87(4): 1409-1439.
[30] DRUCKER D J. The Cardiovascular Biology of Glucagon-like Peptide-1 [J]. Cell Metab, 2016, 24(1): 15-30.
[31] NAUCK M A, MEIER J J. Incretin hormones: Their role in health and disease [J]. Diabetes Obes Metab, 2018, 20 Suppl 1: 5-21.
[32] YUSTA B, BAGGIO L L, ESTALL J L, et al. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress [J]. Cell Metab, 2006, 4(5): 391-406.
[33] NAGORSEN D, BAEUERLE P A. Immunomodulatory therapy of cancer with T cell-engaging BiTE antibody blinatumomab [J]. Exp Cell Res, 2011, 317(9): 1255-1260.
[34] PIAO G, YOON S H, HAN D S, PARK H. Ion-Enhanced Conversion of CO(2) into Formate on Porous Dendritic Bismuth Electrodes with High Efficiency and Durability [J]. ChemSusChem, 2020, 13(4): 698-706.
[35] USSHER J R, DRUCKER D J. Cardiovascular biology of the incretin system [J]. Endocr Rev, 2012, 33(2): 187-215.
[36] MUOIO D M. Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock [J]. Cell, 2014, 159(6): 1253-1262.
[37] TOLHURST G, HEFFRON H, LAM Y S, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2 [J]. Diabetes, 2012, 61(2): 364-371.
[38] THOMAS C, GIOIELLO A, NORIEGA L, et al. TGR5-mediated bile acid sensing controls glucose homeostasis [J]. Cell Metab, 2009, 10(3): 167-177.
[39] MIHAYLOVA M M, SHAW R J. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism [J]. Nat Cell Biol, 2011, 13(9): 1016-1023.
[40] PAPANICOLAOU D A, MULLEN N, KYROU I, NIEMAN L K. Nighttime salivary cortisol: a useful test for the diagnosis of Cushing's syndrome [J]. J Clin Endocrinol Metab, 2002, 87(10): 4515-4521.
[41] KIM J, YANG G, KIM Y, et al. AMPK activators: mechanisms of action and physiological activities [J]. Exp Mol Med, 2016, 48(4): e224.
[42] YIN J, XING H, YE J. Efficacy of berberine in patients with type 2 diabetes mellitus [J]. Metabolism, 2008, 57(5): 712-717.
[43] YANG Q, LI K, LI D, et al. Effects of fine particulate matter on the ocular surface: An in vitro and in vivo study [J]. Biomed Pharmacother, 2019, 117: 109177.
[44] SCHWEIGER M, ROMAUCH M, SCHREIBER R, et al. Corrigendum: Pharmacological inhibition of adipose triglyceride lipase corrects high-fat diet-induced insulin resistance and hepatosteatosis in mice [J]. Nat Commun, 2017, 8: 15490.
[45] MURRAY R D, MELMED S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly [J]. J Clin Endocrinol Metab, 2008, 93(8): 2957-2968.
[46] LEE Y S, KIM W S, KIM K H, et al. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states [J]. Diabetes, 2006, 55(8): 2256-2264.
[47] BAUR J A, PEARSON K J, PRICE N L, et al. Resveratrol improves health and survival of mice on a high-calorie diet [J]. Nature, 2006, 444(7117): 337-342.
[48] LAGOUGE M, ARGMANN C, GERHART-HINES Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha [J]. Cell, 2006, 127(6): 1109-1122.
[49] UM J H, PARK S J, KANG H, et al. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol [J]. Diabetes, 2010, 59(3): 554-563.
[50] HEWLINGS S J, KALMAN D S. Curcumin: A Review of Its Effects on Human Health [J]. Foods, 2017, 6(10).
[51] KIM J H, PARK J M, KIM E K, et al. Curcumin stimulates glucose uptake through AMPK-p38 MAPK pathways in L6 myotube cells [J]. J Cell Physiol, 2010, 223(3): 771-778.
[52] CHUENGSAMARN S, RATTANAMONGKOLGUL S, LUECHAPUDIPORN R, et al. Curcumin extract for prevention of type 2 diabetes [J]. Diabetes Care, 2012, 35(11): 2121-2127.
[53] ZHANG D W, FU M, GAO S H, LIU J L. Curcumin and diabetes: a systematic review [J]. Evid Based Complement Alternat Med, 2013, 2013: 636053.
[54] HAYASAKA M, OGASAWARA H, HOTTA Y, et al. Nutritional assessment using stable isotope ratios of

carbon and nitrogen in the scalp hair of geriatric patients who received enteral and parenteral nutrition formulas [J]. Clin Nutr, 2017, 36(6): 1661-1668.
[55] RAU K M, SU Y L, LI S H, et al. High expression of endoglin in primary breast cancer may predict response to neoadjuvant chemotherapy [J]. Mol Med Rep, 2017, 16(5): 7185-7190.
[56] ARENAS-HUERTERO F, ZARAGOZA-OJEDA M, SáNCHEZ-ALARCóN J, et al. Involvement of Ahr Pathway in Toxicity of Aflatoxins and Other Mycotoxins [J]. Front Microbiol, 2019, 10: 2347.
[57] ATTELE A S, WU J A, YUAN C S. Ginseng pharmacology: multiple constituents and multiple actions [J]. Biochem Pharmacol, 1999, 58(11): 1685-1693.
[58] CHRISTENSEN L P. Ginsenosides chemistry, biosynthesis, analysis, and potential health effects [J]. Adv Food Nutr Res, 2009, 55: 1-99.
[59] TOYANG N J, KRAUSE M A, FAIRHURST R M, et al. Antiplasmodial activity of sesquiterpene lactones and a sucrose ester from Vernonia guineensis Benth. (Asteraceae) [J]. J Ethnopharmacol, 2013, 147(3): 618-621.
[60] DU Z, ZHANG L, RAN J, et al. Exploring the target points and mechanisms of Compound Danshen Dripping Pills in treating diabetic nephropathy based on network pharmacology and molecular docking technology [J]. Gen Physiol Biophys, 2026, 45(1): 19-31.
[61] LI Y, YAO J, HAN C, et al. Quercetin, Inflammation and Immunity [J]. Nutrients, 2016, 8(3): 167.
[62] JEONG S M, KANG M J, CHOI H N, et al. Quercetin ameliorates hyperglycemia and dyslipidemia and improves antioxidant status in type 2 diabetic db/db mice [J]. Nutr Res Pract, 2012, 6(3): 201-207.
[63] WARZAK D A, JOHNSON S A, ELLERSIECK M R, et al. Effects of post-weaning diet on metabolic parameters and DNA methylation status of the cryptic promoter in the A(vy) allele of viable yellow mice [J]. J Nutr Biochem, 2015, 26(6): 667-674.
[64] CURRENTI W, BUSCEMI S, CINCIONE R I, et al. Time-Restricted Feeding and Metabolic Outcomes in a Cohort of Italian Adults [J]. Nutrients, 2021, 13(5).
[65] SHABBIR U, RUBAB M, DALIRI E B, et al. Curcumin, Quercetin, Catechins and Metabolic Diseases: The Role of Gut Microbiota [J]. Nutrients, 2021, 13(1).
[66] AHN J, LEE H, KIM S, et al. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways [J]. Biochem Biophys Res Commun, 2008, 373(4): 545-549.
[67] YANG C S, WANG H. Cancer Preventive Activities of Tea Catechins [J]. Molecules, 2016, 21(12).
[68] WU L Y, JUAN C C, HWANG L S, et al. Green tea supplementation ameliorates insulin resistance and increases glucose transporter IV content in a fructose-fed rat model [J]. Eur J Nutr, 2004, 43(2): 116-124.
[69] LEVINE D Z, IACOVITTI M, ROBERTSON S J, MOKHTAR G A. Modulation of single-nephron GFR in the db/db mouse model of type 2 diabetes mellitus [J]. Am J Physiol Regul Integr Comp Physiol, 2006, 290(4): R975-981.
[70] NAVEED M, HEJAZI V, ABBAS M, et al. Chlorogenic acid (CGA): A pharmacological review and call for further research [J]. Biomed Pharmacother, 2018, 97: 67-74.
[71] AVATAPALLE H B, BANERJEE I, SHAH S, et al. Abnormal Neurodevelopmental Outcomes are Common in Children with Transient Congenital Hyperinsulinism [J]. Front Endocrinol (Lausanne), 2013, 4: 60.
[72] WANG Q A, SCHERER P E. Human Beige Adipocytes: Epiphenomenon or Drivers of Metabolic Improvements? [J]. Trends Endocrinol Metab, 2016, 27(5): 244-246.
[73] LI Y, XU S, MIHAYLOVA M M, et al. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice [J]. Cell Metab, 2011, 13(4): 376-388.
[74] FRIEDRICHSEN M, MORTENSEN B, PEHMøLLER C, et al. Exercise-induced AMPK activity in skeletal muscle: role in glucose uptake and insulin sensitivity [J]. Mol Cell Endocrinol, 2013, 366(2): 204-214.