

# MicroRNA-Regulated Network Pharmacology of Five Traditional Antidiabetic Medicinal Plants: A Systems Biology Hypothesis Linking Phytochemicals to Type 2 Diabetes Signaling

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Received: October 30, 2025; Revised: January 30, 2026; Accepted: February 8, 2026; April 8, 2026

## Abstract

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by insulin resistance, chronic low-grade inflammation,  $\beta$ -cell dysfunction, oxidative stress, and progressive tissue damage. Emerging evidence highlights microRNAs (miRNAs) as key epigenetic regulators integrating metabolic and inflammatory signaling networks. However, the miRNA-centered mechanisms underlying many traditional antidiabetic medicinal plants remain largely unexplored. The present review proposes a systems biology-based, hypothesis-driven framework linking bioactive phytochemicals from five traditional medicinal plants—*Urtica dioica* (nettle), *Eryngium spp.* (Boughnagh), *Cinnamomum spp.* (Cinnamon), *Silybum marianum* (milk thistle), and *Citrullus colocynthis* (bitter apple)—to microRNA-regulated signaling networks involved in T2DM pathophysiology. A narrative systems biology approach was employed based on the integration of phytochemical evidence (polyphenols, flavonoids, lignans, triterpenoids, and saponins) with experimentally validated miRNA–target interactions reported in metabolic, inflammatory, and oxidative stress–related diseases. Indirect mechanistic inference was used to map plant-derived compounds onto key miRNA nodes and downstream signaling pathways. The selected medicinal plants are hypothesized to modulate a convergent set of miRNAs, including miR-155, miR-146a, miR-21, miR-103/107, miR-375, miR-34a, miR-122, and miR-29 family. These miRNAs collectively regulate major signaling axes implicated in T2DM, including NF- $\kappa$ B, PI3K/Akt, AMPK, TGF- $\beta$ /Smad, and Nrf2/ARE pathways. The integrative network suggests that these phytochemicals may act as multi-target epigenetic modulators rather than single-target agents, potentially restoring metabolic homeostasis and attenuating diabetic complications. This review introduces a hypothesis-driven microRNA-regulated network pharmacology framework for five traditional antidiabetic medicinal plants, providing a conceptual bridge between phytochemistry and systems-level epigenetic regulation in T2DM.

**Keywords:** Medicinal plants; microRNA; network pharmacology; systems biology; Type 2 diabetes



## Introduction

Diabetes mellitus (DM) comprises a heterogeneous group of metabolic disorders characterized primarily by chronic hyperglycemia (1). The pathogenesis of DM is broadly classified into two major forms: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The T1DM is defined by an absolute deficiency of insulin secretion resulting from autoimmune-mediated destruction of pancreatic  $\beta$ -cells, whereas T2DM, which accounts for more than 90% of all diabetes cases worldwide, is characterized by peripheral insulin resistance accompanied by an inadequate compensatory insulin secretory response (2, 3). The etiology of T2DM is multifactorial and involves a complex interplay between genetic predisposition, epigenetic regulation, gut microbiota dysbiosis, and acquired risk factors, such as obesity, physical inactivity, and unhealthy dietary patterns (4). Persistent hyperglycemia leads to endothelial dysfunction, oxidative stress, and chronic low-grade inflammation, thereby contributing to the progression of severe diabetic complications. These include microvascular complications, such as diabetic nephropathy, retinopathy, and neuropathy, as well as macrovascular complications including cardiovascular and cerebrovascular diseases. Collectively, these complications represent major determinants of increased morbidity, mortality, and reduced quality of life in patients with DM (5). At the molecular level, the pathophysiology of DM is associated with profound alterations in gene expression, in which the microRNA-mediated regulatory network plays a central role (6, 7). MicroRNAs are small non-coding RNA molecules, approximately 22 nucleotides in length, that regulate gene expression post-transcriptionally by repressing translation or promoting degradation of target messenger RNAs (mRNAs) in a sequence-specific manner (8). In the diabetic state, this tightly regulated

epigenetic network becomes dysregulated, contributing to widespread metabolic and inflammatory disturbances. In particular, the downregulation of miRNAs that normally restrain inflammatory signaling pathways leads to sustained activation of pro-inflammatory cascades and excessive production of cytokines, thereby exacerbating insulin resistance and tissue dysfunction (9, 10). Conversely, aberrant upregulation of miRNAs targeting key components of the insulin signaling pathway—including the insulin receptor (INSR) and downstream effectors—further impairs insulin sensitivity at the cellular level (10). Collectively, these dysregulated miRNA profiles establish a self-amplifying molecular feedback loop that integrates metabolic stress, inflammation, and insulin signaling impairment, thereby contributing to the initiation and progression of diabetic pathology (11). Current pharmacological therapies for DM, including metformin, sulfonylureas, and glucagon-like peptide-1 (GLP-1) receptor agonists, exert their therapeutic effects through distinct mechanisms, such as suppression of hepatic gluconeogenesis, stimulation of insulin secretion, and improvement of peripheral insulin sensitivity (12-14). Although these agents demonstrate well-established clinical efficacy, their long-term use is frequently associated with adverse effects, progressive decline in therapeutic responsiveness (secondary failure), and limited capacity to fully prevent the onset and progression of chronic diabetic complications (15). These limitations highlight the need for complementary or alternative therapeutic strategies with improved safety profiles and broader mechanistic coverage. In this context, medicinal plants—long utilized in traditional, regional, and indigenous medical systems, represent a rich source of structurally diverse bioactive phytochemicals with potential therapeutic relevance in complex metabolic disorders, such as DM (16). In contrast to conventional single-target drugs, plant-derived

extracts typically exert pleiotropic biological effects through the simultaneous modulation of multiple interconnected signaling pathways. This multitarget pharmacological behavior is particularly advantageous in the context of diabetes, a multifactorial disease driven by dysregulated metabolic, inflammatory, and oxidative stress networks (17). However, the molecular mechanisms underlying the broad biological activities of these medicinal plants remain incompletely characterized. Accordingly, the present review aims to systematically explore the signaling pathways regulated by five widely used antidiabetic medicinal plants in traditional Persian medicine—*Urtica dioica* (nettle), *Eryngium* spp., *Cinnamomum* spp. (Cinnamon), *Silybum marianum* (milk thistle), and *Citrullus colocynthis* (bitter apple)—with particular emphasis on microRNAs as central epigenetic regulators of metabolic and inflammatory homeostasis. According to converging evidence from phytochemical profiling and the established role of microRNA-regulated signaling networks in the pathophysiology of T2DM, we propose that the therapeutic effects of these plants are unlikely to be mediated by single-target pharmacological mechanisms. Instead, they may act through coordinated, multi-target modulation of microRNA-centered regulatory networks. In this hypothesis-driven framework, bioactive phytochemicals—including polyphenols, flavonoids, lignans, triterpenoid saponins, and cinnamaldehyde derivatives—are suggested to indirectly modulate key microRNAs implicated in T2DM, including those involved in inflammatory signaling (e.g., miR-155, miR-146a), insulin resistance (e.g., miR-103/107, miR-21),  $\beta$ -cell dysfunction and survival (e.g., miR-375, miR-34a, miR-7), oxidative stress regulation (e.g., miR-200a), and metabolic homeostasis (e.g., miR-122, miR-29 family). These microRNAs converge on major signaling pathways central to T2DM progression, including NF- $\kappa$ B, PI3K/Akt, AMPK, TGF- $\beta$ /Smad, and

Nrf2/ARE. Collectively, we hypothesize that these medicinal plants function as natural multi-component network modulators capable of partially reprogramming dysregulated epigenetic and signaling landscapes in T2DM, thereby simultaneously targeting hyperglycemia, insulin resistance, chronic inflammation, oxidative stress, and diabetic complications.

## Methods

This study was designed as a narrative conceptual review based on a structured and comprehensive literature search of the scientific evidence. A systematic search was conducted across major electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant publications available up to 2026. To capture recent advances in the field, particular emphasis was placed on studies published from 2018 onward. The literature search strategy was developed using combinations of controlled vocabulary and free-text keywords, including but not limited to: “diabetes mellitus,” “type 2 diabetes,” “microRNA,” “miRNA,” “medicinal plants,” “phytochemicals,” “*Urtica dioica*,” “*Eryngium*,” “*Cinnamomum*,” “*Silybum marianum*,” “*Citrullus colocynthis*,” “insulin signaling,” “inflammation,” “oxidative stress,” and “signal transduction.” Boolean operators (AND/OR) were applied to refine and optimize search sensitivity and specificity. Eligible studies included original research articles, experimental studies, and review articles investigating the molecular mechanisms, signaling pathways, and/or microRNA-associated effects of the selected medicinal plants in the context of DM. Priority was given to peer-reviewed publications with robust experimental design and clear mechanistic insights. Studies lacking sufficient molecular or mechanistic relevance to the scope of this review were excluded. The retrieved literature was critically evaluated and qualitatively synthesized to generate an integrated framework describing the signaling

pathways modulated by the selected medicinal plants, with a particular focus on microRNA-mediated regulatory mechanisms in glucose homeostasis, insulin signaling, inflammation, and oxidative stress.

## Results

### MicroRNA-Regulated Network Pharmacology of Selected Antidiabetic Medicinal Plants

#### *Urtica* spp. (Nettle)

##### Phytochemical Profile and Bioactive Constituents

*Urtica* spp. (nettle) has long been recognized in traditional medicine for its anti-inflammatory, diuretic, and anti-arthritic properties and is currently considered one of the most promising medicinal plants for the phytotherapeutic management of T2DM (18). The genus *Urtica* comprises approximately 50 species, among which *Urtica dioica* and *Urtica urens* are the most widely distributed and extensively studied (19). The therapeutic efficacy of *Urtica* is attributed to a synergistic phytochemical network rather than a single active constituent. Both aerial and root parts contain diverse bioactive metabolites, including flavonoids (notably quercetin and kaempferol glycosides), phenolic acids (e.g., caffeic and chlorogenic acid derivatives), phytosterols (particularly  $\beta$ -sitosterol), lectins, such as *Urtica dioica* agglutinin (UDA), and trace elements, including chromium (20-23). Collectively, these compounds contribute to its pleiotropic pharmacological profile.

##### Metabolic and Insulin-Signaling Effects

The antidiabetic effects of *Urtica* involve multiple complementary mechanisms. In the gastrointestinal tract, phenolic constituents inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase, thereby delaying carbohydrate digestion and attenuating postprandial hyperglycemia (24, 25). At the

cellular level, flavonoids, such as quercetin, enhance insulin signaling via activation of the PI3K/Akt pathway, promoting IRS-1 phosphorylation and GLUT4 translocation, which increases peripheral glucose uptake and improves insulin sensitivity (26, 27). In parallel, *Urtica* exerts anti-inflammatory effects through inhibition of the NF- $\kappa$ B signaling cascade. Specifically, suppression of I $\kappa$ B kinase (IKK) activity prevents NF- $\kappa$ B nuclear translocation and reduces the expression of pro-inflammatory cytokines, including TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , thereby mitigating inflammation-induced insulin resistance (28). In addition, chromium may further enhance INSR kinase activity via chromodulin-mediated potentiation of insulin signaling (29).

##### microRNA-Mediated Regulatory Effects

The multitarget pharmacological actions of *Urtica* are likely associated with indirect modulation of diabetes-related microRNA networks. Rather than directly targeting microRNAs, these effects appear to be mediated through upstream regulation of inflammatory, oxidative, and metabolic signaling pathways (30). The proposed miRNA-centered mechanisms of *Urtica dioica* are summarized in Figure 1, highlighting its potential indirect modulation of miRNAs involved in inflammation, insulin resistance, hepatic metabolism, and oxidative stress.

Suppression of NF- $\kappa$ B signaling may restore the functional balance of the miR-146a regulatory axis (IRAK1/TRAF6), thereby reinforcing endogenous anti-inflammatory feedback mechanisms in pancreatic islets (31-33). In addition, preservation of miR-375 expression supports  $\beta$ -cell survival and insulin secretion, whereas attenuation of endoplasmic reticulum stress may counteract miR-204 upregulation associated with  $\beta$ -cell dysfunction (34, 35). At the systemic level, *Urtica* may influence key metabolic microRNAs, including miR-223

(GLUT4-mediated glucose uptake), miR-21 (PTEN/PI3K/Akt axis), and miR-200a (Nrf2/ARE antioxidant pathway), collectively improving insulin responsiveness and oxidative stress control (36-42). Endothelial protection may involve restoration of miR-126 and miR-145, contributing to vascular homeostasis (43-47), whereas regulation of miR-29 and miR-122 may attenuate fibrosis and improve lipid metabolism in renal and hepatic tissues (48-55).

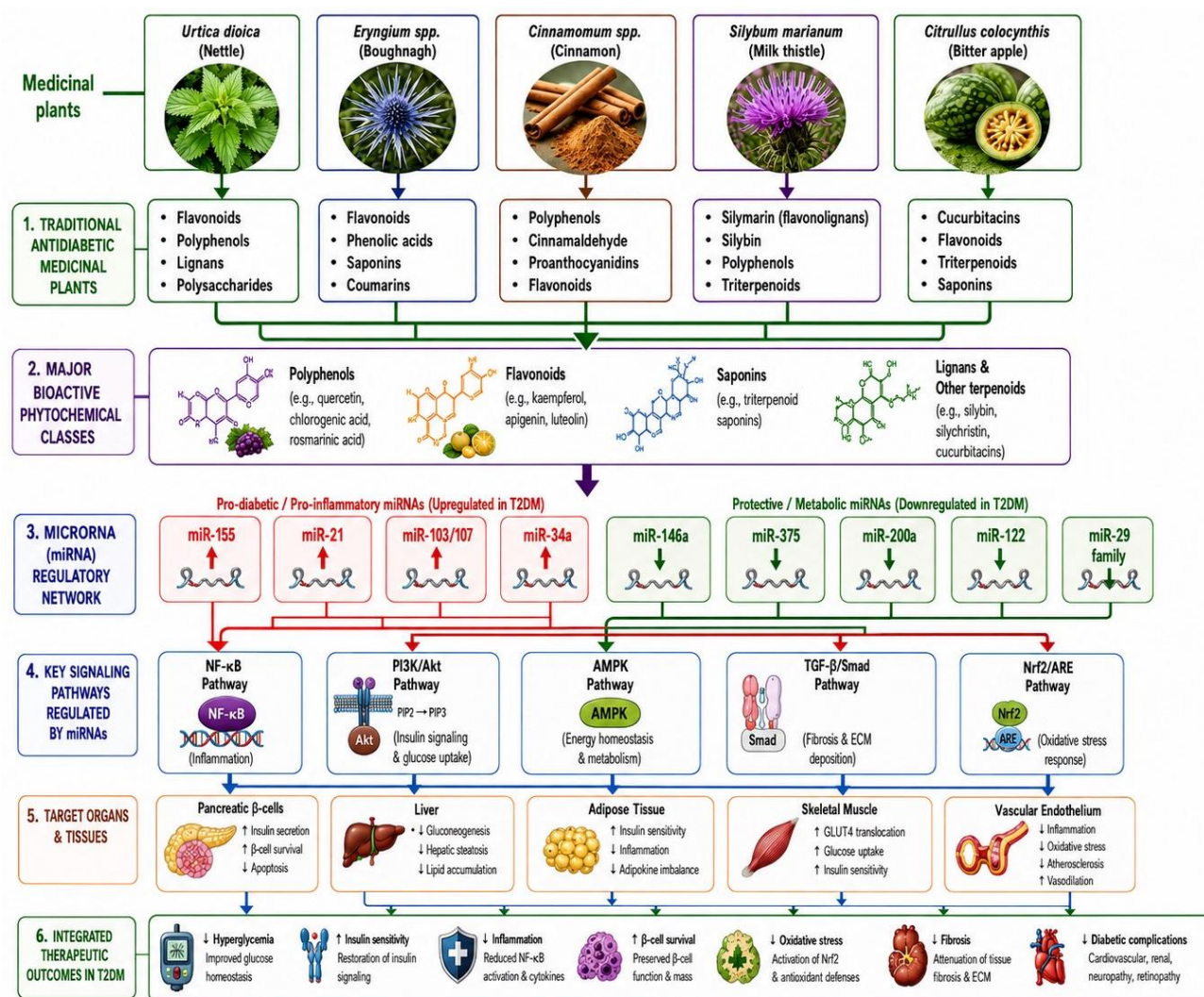
### Cellular Stress and Senescence Pathways

By reducing oxidative stress and chronic inflammation, *Urtica* may also modulate senescence-associated microRNAs, particularly miR-34a, a p53-responsive regulator of apoptosis and mitochondrial dysfunction (56-59). Concurrently, restoration of the let-7 family may contribute to improved cellular differentiation, insulin sensitivity, and metabolic stability in diabetic conditions (60-62). Table 1 presents the predicted microRNA-mediated regulatory network of *Urtica dioica* in T2DM.

**Table 1.** Predicted microRNA-mediated regulatory network of *Urtica dioica* in T2DM

| microRNA      | Role in T2DM pathophysiology (in untreated state)                           | Hypothesized modulation by <i>Urtica dioica</i>                           | Main signaling pathway              |
|---------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------|
| miR-146a      | Downregulated; contributes to NF-κB overactivation and chronic inflammation | Upregulated; suppresses TRAF6/IRAK1 signaling and inflammatory response   | NF-κB                               |
| miR-375       | Dysregulated; decreased expression promotes β-cell apoptosis                | Stabilization/restoration; supports β-cell survival and insulin secretion | β-cell function/insulin secretion   |
| miR-126       | Reduced; associated with endothelial dysfunction and vascular complications | Upregulated; suppresses VCAM-1 and improves endothelial integrity         | Endothelial function/VEGF signaling |
| miR-21        | Upregulated; suppresses PTEN and impairs insulin signaling                  | Downregulated; restores PTEN activity and improves insulin sensitivity    | PI3K/Akt                            |
| miR-29 family | Downregulated; promotes extracellular matrix accumulation and fibrosis      | Upregulated; inhibits pro-fibrotic gene expression                        | TGF-β/anti-fibrotic pathway         |
| miR-223       | Dysregulated; impairs GLUT4-mediated glucose uptake                         | Modulated toward physiological levels; improves glucose transport         | Glucose uptake/GLUT4                |
| miR-200a      | Upregulated; suppresses Nrf2-mediated antioxidant defense                   | Downregulated; restores Nrf2 activity and antioxidant response            | Nrf2/ARE                            |
| miR-122       | Reduced; associated with hepatic steatosis and lipid dysregulation          | Upregulated; improves hepatic lipid metabolism                            | Hepatic lipid metabolism            |
| let-7 family  | Downregulated; linked to metabolic instability and impaired homeostasis     | Upregulated; supports metabolic regulation and cellular homeostasis       | Ras/metabolic regulation            |

|         |                                                                                |                                                                                      |                            |
|---------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------|
| miR-204 | Upregulated; promotes $\beta$ -cell apoptosis via ER stress pathways           | Downregulated (putative); alleviates ER stress and oxidative damage                  | ER stress/UPR              |
| miR-34a | Upregulated; associated with cellular senescence and mitochondrial dysfunction | Downregulated (putative); mediated via AMPK/Nrf2 activation                          | p53/oxidative stress       |
| miR-145 | Downregulated; contributes to vascular dysfunction and plaque instability      | Upregulated (putative); improves vascular homeostasis and reduces AGE–RAGE signaling | AGE–RAGE/vascular function |



**Figure 1.** Network-based phytotherapy and microRNA-regulated network pharmacology model of five traditional antidiabetic medicinal plants in T2DM.

This schematic represents a systems biology framework underlying the multi-target antidiabetic effects of five traditional medicinal plants (*Urtica dioica*, *Eryngium spp.*, *Cinnamomum spp.*, *Silybum marianum*, and *Citrullus colocynthis*). The model illustrates plant-derived bioactive phytochemical classes, including polyphenols, flavonoids, triterpenoid saponins, lignans, and cucurbitacins, as upstream modulators of epigenetic regulation in key metabolic organs, including pancreatic  $\beta$ -cells, liver, adipose tissue, skeletal muscle, and vascular endothelium. Central to this framework is a microRNA (miRNA)-mediated regulatory network comprising

pro-diabetic miRNAs (e.g., miR-155, miR-21, miR-103/107, and miR-34a) and protective metabolic miRNAs (e.g., miR-146a, miR-375, miR-200a, miR-122, and the miR-29 family). These miRNAs integrate major pathological processes in T2DM, including inflammation, insulin resistance,  $\beta$ -cell dysfunction, oxidative stress, and metabolic dysregulation. Downstream of this regulatory layer, the miRNA network converges on key signaling pathways such as NF- $\kappa$ B, JAK/STAT, PI3K/Akt, AMPK, Nrf2/ARE, and TGF- $\beta$ /Smad, which collectively modulate metabolic homeostasis across target organs. Overall, the model emphasizes a multi-target, network-based pharmacological mechanism in which phytochemical combinations from traditional medicinal plants act as epigenetic regulators, restoring insulin sensitivity, attenuating inflammation and oxidative stress, and reducing the progression of diabetic complications through coordinated modulation of miRNA-centered signaling networks.

### ***Eryngium* spp. (Booghnaagh)**

#### **Phytochemical Profile and Bioactive Constituents**

The genus *Eryngium* (family Apiaceae), commonly known as Booghnaagh or Zool in traditional Persian medicine, is among the most extensively used medicinal plants for the management of DM (63). Unlike typical soft-stemmed members of Apiaceae, *Eryngium* species are characterized by a rigid, leathery, and spiny morphology with compact globular inflorescences surrounded by blue, silver, or purple bracts (64). The genus comprises approximately 250 species distributed across diverse ecological regions worldwide, with more than ten species reported in Iran. Among these, *Eryngium billardieri* and related taxa are most commonly cited in traditional Iranian medicine as “Booghnaagh” (64). The phytochemical profile of *Eryngium* is dominated by triterpenoid saponins and a wide range of phenolic compounds, including flavonoids (e.g., quercetin and rutin) and phenolic acids, such as rosmarinic and caffeic acid. Inulin-type fructans are highly concentrated in the roots, along with minor polyacetylenes and volatile terpenoids, collectively forming a complex synergistic phytochemical matrix (65, 66). This chemical diversity underlies its broad pharmacological potential.

#### **Metabolic and Antidiabetic Mechanisms**

The antidiabetic effects of *Eryngium* are mediated through multiple complementary pathways. Triterpenoid saponins exert insulinotropic effects via modulation of ATP-sensitive potassium (KATP) channels in pancreatic  $\beta$ -cells, leading to membrane

depolarization,  $\text{Ca}^{2+}$  influx, and enhanced insulin secretion. Concurrently, phenolic constituents protect  $\beta$ -cells against glucotoxicity- and lipotoxicity-induced dysfunction, preserving insulin secretory capacity (63). In addition, *Eryngium* attenuates oxidative stress and inflammation, key contributors to insulin resistance. Flavonoids and phenolic acids scavenge reactive oxygen species (ROS) and activate the Nrf2/ARE pathway, increasing antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT). Simultaneously, suppression of NF- $\kappa$ B signaling reduces pro-inflammatory cytokines including TNF- $\alpha$  and IL-6, thereby improving insulin sensitivity (63, 64, 67). Within the gastrointestinal tract, inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase delays carbohydrate absorption and reduces postprandial hyperglycemia (68). Inulin further acts as a prebiotic, promoting short-chain fatty acid (SCFA) production and stimulating GLP-1 secretion, thereby enhancing glucose-dependent insulin release (69). At the hepatic level, *Eryngium* may suppress gluconeogenesis via downregulation of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK). Additionally, activation of the PI3K/Akt pathway enhances GLUT4 translocation in peripheral tissues, improving glucose uptake and systemic insulin sensitivity (27).

#### **MicroRNA-Related Mechanistic Hypothesis**

Despite strong experimental evidence supporting the antidiabetic effects of *Eryngium*, no direct studies have yet examined its effects on microRNA expression profiles in diabetes-related

systems. However, its phytochemical constituents—particularly quercetin, caffeic acid, and rosmarinic acid—have been shown in independent studies to modulate key diabetes-associated microRNAs (70-73). Accordingly, as illustrated in Figure 1, part of the antidiabetic activity of *Eryngium* may be mediated through indirect epigenetic regulation of microRNA networks, primarily via upstream modulation of inflammatory, oxidative, and metabolic pathways.

#### Inflammation-Related microRNA Modulation

One proposed mechanism involves suppression of miR-155, a central pro-inflammatory microRNA that enhances JAK/STAT and NF- $\kappa$ B signaling through targeting SOCS1 (74-77). Downregulation of miR-155 may therefore attenuate chronic inflammatory responses. Conversely, upregulation of miR-146a may establish a negative feedback loop by inhibiting NF- $\kappa$ B activity, thereby limiting excessive inflammation (78). Furthermore, combined evidence suggests that microbial metabolites, such as butyrate, particularly when co-administered with inulin, can increase miR-146a-5p and miR-9-5p expression while suppressing TLR2/4, NF- $\kappa$ B1, and inflammasome components. These effects collectively reduce pyroptosis via targeting of TLR2 and NF- $\kappa$ B signaling pathways (79). Although promising, the direct relevance of these mechanisms to *Eryngium* phytocomplexes remains unconfirmed.

#### $\beta$ -Cell Protection and Stress-Related microRNAs

**Table 2.** Predicted microRNA-mediated regulatory network of *Eryngium spp.* in T2DM

| microRNA | Role in T2DM pathophysiology (untreated state)                                                   | Hypothesized modulation by <i>Eryngium spp.</i>                                                    | Main signaling pathway                   |
|----------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|------------------------------------------|
| miR-146a | Downregulated; associated with NF- $\kappa$ B overactivation and chronic inflammation            | Upregulation via suppression of NF- $\kappa$ B signaling mediated by flavonoids and phenolic acids | NF- $\kappa$ B                           |
| miR-375  | Dysregulated; reduced expression promotes $\beta$ -cell apoptosis and impaired insulin secretion | Stabilization/restoration through reduction of oxidative stress and $\beta$ -cell protection       | $\beta$ -cell survival/insulin secretion |

Reduction of oxidative stress may indirectly suppress miR-34a, a stress-responsive microRNA involved in  $\beta$ -cell apoptosis and dysfunction (56-59). This effect is likely mediated through ROS scavenging, Nrf2 activation, and anti-inflammatory signaling. In parallel, maintenance of miR-375 expression may support  $\beta$ -cell identity and insulin secretion, although direct evidence in *Eryngium* is currently lacking (80).

#### Nrf2/miR-200a Regulatory Axis

Another proposed mechanism involves miR-200a, which negatively regulates the Nrf2 antioxidant pathway (42). Suppression of miR-200a could theoretically enhance endogenous antioxidant defenses. However, this interaction has only been confirmed for isolated compounds and requires further validation in the context of the full *Eryngium* phytochemical matrix.

#### Additional microRNA Networks and Systemic Effects

The pleiotropic effects of *Eryngium* on inflammation, oxidative stress, and metabolic regulation may secondarily influence additional diabetes-associated microRNAs, including miR-122 (51, 54), miR-33a/b (81, 82), and members of the miR-29 family (48-50). These effects are likely indirect, mediated by improved hepatic metabolic function, activation of AMP-activated protein kinase (AMPK), and suppression of fibrotic signaling pathways. Table 2 presents the predicted microRNA-mediated regulatory network of *Eryngium spp.* in T2DM.

|                       |                                                                                                 |                                                                                                                |                                     |
|-----------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------|
| miR-155               | Upregulated; enhances inflammatory responses and tissue injury                                  | Downregulation via inhibition of pro-inflammatory signaling pathways (NF- $\kappa$ B, AP-1) by polyphenols     | NF- $\kappa$ B/AP-1                 |
| miR-29 family (a/b/c) | Downregulated; contributes to extracellular matrix accumulation and organ fibrosis              | Upregulation via attenuation of TGF- $\beta$ /Smad signaling, potentially mediated by quercetin and kaempferol | TGF- $\beta$ /anti-fibrotic pathway |
| miR-200a              | Upregulated; suppresses Nrf2 signaling and weakens antioxidant defense                          | Downregulation leading to restoration of Nrf2/ARE antioxidant response                                         | Nrf2/ARE                            |
| miR-122               | Downregulated; associated with hepatic lipid accumulation and dyslipidemia                      | Upregulation via AMPK activation and improved lipid metabolism                                                 | Hepatic lipid metabolism/AMPK       |
| miR-34a/b             | Upregulated; promotes cellular senescence and $\beta$ -cell/ endothelial apoptosis              | Downregulation through antioxidant effects and potential activation of SIRT1 signaling                         | p53/SIRT1/oxidative stress          |
| miR-221/222           | Upregulated; associated with pathological angiogenesis and vascular smooth muscle proliferation | Downregulation potentially reducing VEGF-driven abnormal angiogenesis                                          | VEGF/angiogenesis                   |

### *Cinnamomum* spp. (Cinnamon)

#### Phytochemical Profile and Bioactive Constituents

Cinnamon is the dried inner bark of trees belonging to the genus *Cinnamomum* (family Lauraceae) and represents one of the most important medicinal-food spices with a long history in traditional and modern pharmacopoeias (83). Beyond its culinary applications, cinnamon has been extensively investigated as an adjunctive agent in the management of dysglycemia and metabolic syndrome, particularly T2DM (84). From a pharmacognostic perspective, distinguishing between commercial species is of clinical relevance. *Cinnamomum verum* (*C. zeylanicum*), known as Ceylon cinnamon or “true cinnamon,” differs substantially from cassia species, including *C. burmannii*, *C. cassia*, *C. loureiroi*, and *C. citriodorum* (85). A key distinction lies in coumarin content, which is significantly higher in cassia species and may pose hepatotoxicity risks upon long-term high-dose consumption; therefore, *C. verum* is generally preferred for therapeutic applications (85). The phytocomplex of cinnamon is highly complex and consists of volatile and non-volatile fractions. The volatile

fraction is dominated by cinnamaldehyde (60–90%), along with eugenol and cinnamic acid derivatives, contributing to antimicrobial, anti-inflammatory, and organoleptic properties (86). The non-volatile fraction contains key bioactive compounds, including type A proanthocyanidins and methylhydroxychalcone polymers (MHCP), which are proposed to exert insulin-mimetic effects. Additional constituents, such as catechin, epicatechin, quercetin, and kaempferol, further contribute to antioxidant and anti-inflammatory activity. Trace elements, including manganese, calcium, iron, and chromium, may also support insulin signaling, potentially via glucose tolerance factor (GTF)-related mechanisms (86).

#### Insulin Signaling and Metabolic Regulation

Experimental evidence suggests that cinnamon and its bioactive constituents modulate multiple pathways involved in glucose homeostasis. One proposed mechanism involves enhancement of insulin signaling through increased phosphorylation of the INSR and downstream effectors. This effect has been partly attributed to inhibition of negative regulators, such as protein tyrosine phosphatase 1B (PTP1B), resulting in prolonged INSR activation; however, clinical

validation remains limited (87, 88). In addition, activation of AMPK has been proposed as an insulin-independent mechanism.

Cinnamaldehyde and polyphenolic compounds may activate AMPK by modulating cellular energy status or upstream kinases, leading to increased glucose uptake and suppression of gluconeogenesis (89, 90). Cinnamon may also influence the Akt signaling pathway, where enhanced Akt activity inhibits glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), thereby promoting glycogen synthesis and storage (91, 92). However, most evidence is derived from preclinical models, and translational relevance requires further confirmation.

#### Gastrointestinal Effects on Glucose Homeostasis

At the intestinal level, cinnamon polyphenols inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase, thereby delaying carbohydrate digestion and glucose absorption. This mechanism contributes to attenuation of postprandial hyperglycemia and represents one of the most physiologically relevant and well-supported antidiabetic actions of cinnamon (93).

#### microRNA-Mediated Regulatory Effects

Emerging evidence suggests that cinnamon may modulate microRNA networks involved in insulin signaling, inflammation, lipid metabolism, and oxidative stress.

The proposed molecular mechanisms of *Cinnamomum* spp. are illustrated in Figure 1, emphasizing potential miRNA-mediated regulation of insulin signaling, pancreatic  $\beta$ -cell function, inflammation, and oxidative stress.

However, the current body of evidence is primarily derived from preclinical studies, and clinical validation is still lacking. Among the

most studied targets, miR-103 and miR-107 have been implicated in insulin resistance through suppression of INSR expression. Experimental studies indicate that polyphenol-rich cinnamon extracts may reduce the expression of these miRNAs in metabolic tissues, accompanied by improvements in insulin signaling; however, causality in humans has not been established (89, 94-97). Cinnamon polyphenols have also been associated with modulation of miR-223, a microRNA involved in glucose uptake and insulin responsiveness (98). In addition, alterations in miR-122 expression have been reported in animal models, suggesting potential effects on hepatic lipid metabolism and steatosis (99). Nonetheless, translational evidence remains insufficient. From an inflammatory perspective, upregulation of miR-146a has been observed following cinnamaldehyde, a bioactive compound derived from cinnamon, treatment in experimental systems, potentially contributing to negative regulation of NF- $\kappa$ B signaling and attenuation of inflammatory responses (100). Conversely, downregulation of miR-155 has been reported in preclinical models, suggesting a potential anti-inflammatory mechanism (101). However, these effects require confirmation in well-designed clinical trials. Overall, available evidence supports the hypothesis that epigenetic modulation of diabetes-associated miRNAs may contribute to the pleiotropic metabolic effects of cinnamon. Nevertheless, current findings remain predominantly preclinical, and further mechanistic and clinical studies are required to clarify the causal relationships between cinnamon supplementation, miRNA regulation, and metabolic outcomes in T2DM. Table 3 presents the predicted microRNA-mediated regulatory network of *Cinnamomum* spp. in T2DM.

**Table 3.** Predicted microRNA-mediated regulatory network of *Cinnamomum* spp. in T2DM

| microRNA    | Role in T2DM pathophysiology (untreated state)                                                                  | Hypothesized modulation by Cinnamon                                                                                            | Main signaling pathway              |
|-------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| miR-146a    | Downregulated; associated with NF-κB overactivation and chronic low-grade inflammation                          | Upregulation and functional restoration, potentially secondary to reduced inflammatory burden mediated by cinnamon polyphenols | NF-κB                               |
| miR-155     | Upregulated; promotes inflammatory signaling and tissue damage                                                  | Downregulation through attenuation of NF-κB– and JAK/STAT–mediated inflammatory pathways                                       | NF-κB/JAK-STAT                      |
| miR-122     | Downregulated; associated with hepatic lipid accumulation and dyslipidemia                                      | Upregulation via improvement of insulin sensitivity and regulation of lipid metabolism (e.g., SREBP-1c axis)                   | Hepatic lipid metabolism/SREBP-1c   |
| miR-223     | Dysregulated; contributes to low-grade inflammation in metabolic tissues and insulin resistance                 | Modulation toward physiological levels, associated with reduced inflammatory signaling in adipose and hepatic tissues          | NLRP3 inflammasome/inflammation     |
| miR-103/107 | Upregulated; implicated in insulin resistance through targeting caveolin-1 (Cav-1) and impairing INSR signaling | Downregulation, potentially restoring Cav-1 expression and improving insulin signaling sensitivity                             | Insulin signaling/Cav-1/IRS pathway |

### ***Silybum marianum* (Milk thistle)**

#### **Phytochemical Profile and Bioactive Constituents**

Silymarin is an important plant-derived bioactive compound obtained from the seeds and fruits of *Silybum marianum* (milk thistle). It is a complex mixture of flavonolignans, with silybin (also known as silibinin) being the major and most biologically active component. Other constituents of silymarin include silydianin, silychristin, and isosilybin. Due to its diverse pharmacological properties, including antioxidant, anti-inflammatory, hepatoprotective, and cytoprotective effects, silymarin has attracted considerable attention in the prevention and treatment of various pathological conditions (102, 103). Beyond its traditional applications, this species has gained considerable attention in metabolic disorders, particularly T2DM, due to its pleiotropic bioactive profile (104). The principal bioactive complex of *S. marianum* is

silymarin, a lipophilic mixture of flavonolignans predominantly concentrated in the fruits (seeds), accounting for approximately 1.5–3% of dry weight. Silymarin consists of several structural isomers, including silybin (silibinin A and B, the most abundant and biologically active component), isosilybin, silychristin, and silydianin, along with minor flavonoids, such as taxifolin. The plant also contains 20–30% fixed oil rich in unsaturated fatty acids (linoleic and oleic acids), sterols, and other lipophilic constituents that collectively contribute to its pharmacological activity (102, 103).

#### **Pharmacological Mechanisms in Metabolic Regulation**

Silymarin exerts multitarget metabolic effects through complementary mechanisms involved in glucose homeostasis, insulin sensitivity, oxidative stress, and inflammation. At the gastrointestinal level, silymarin may indirectly

attenuate postprandial hyperglycemia by improving systemic insulin sensitivity and modulating carbohydrate metabolism (105). At the cellular level, silymarin enhances insulin signaling by increasing phosphorylation of insulin receptor substrate-1 (IRS-1) and activating the PI3K/Akt pathway. This results in enhanced translocation of GLUT4 to the plasma membrane in skeletal muscle and adipose tissue, thereby improving peripheral glucose uptake and glycemic control (106). Furthermore, silymarin acts as a partial agonist of peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ), a nuclear receptor targeted by thiazolidinedione drugs, playing a central role in adipocyte differentiation, lipid metabolism regulation, and improvement of insulin sensitivity (105-108). In the liver, silymarin suppresses gluconeogenesis through downregulation of key enzymes, including PEPCK and G6Pase. These effects are partly mediated via activation of AMPK, contributing to improved hepatic glucose homeostasis (109). Silymarin also exhibits potent antioxidant and anti-inflammatory activities through activation of the Nrf2 signaling pathway, leading to upregulation of endogenous antioxidant enzymes, such as SOD, CAT, and glutathione peroxidase (GPx). Concurrently, it inhibits NF- $\kappa$ B activation, thereby reducing pro-inflammatory cytokines including TNF- $\alpha$  and IL-6, which collectively protect against insulin resistance and  $\beta$ -cell dysfunction (110, 111). Additionally, silymarin inhibits non-enzymatic protein glycation, contributing to the prevention of long-term diabetic complications such as nephropathy and retinopathy (112).

#### Epigenetic Regulation via microRNAs

The molecular mechanisms underlying the effects of silibinin, the most active constituent of silymarin, on microRNAs in the context of diabetes and its complications represent a relatively new and rapidly evolving area of research. Emerging evidence suggests that part of

the metabolic and anti-inflammatory effects of silymarin may be mediated through the regulation of microRNA expression. Among these, miR-34a and miR-122 have been directly investigated in experimental models (113-115). Downregulation of miR-34a has been associated with increased expression of Bcl-2 and reduced cellular apoptosis, whereas normalization of miR-122 expression contributes to improved lipid homeostasis and attenuation of hepatic steatosis.

In addition, silymarin has been shown to modulate inflammation-related microRNAs, including miR-21 and members of the miR-29 family (116).

As summarized in Figure 1, *Silybum marianum* may influence miRNA-centered regulatory networks involved in hepatic metabolism, inflammation, oxidative stress, and tissue fibrosis, particularly through pathways associated with miR-122, miR-21, and the miR-29 family. Inhibition of miR-21, a well-characterized pro-fibrotic and pro-inflammatory microRNA (40), together with upregulation of miR-29, a negative regulator of extracellular matrix gene expression (48), may represent a plausible mechanism underlying the protective effects of silymarin against chronic diabetic complications, such as nephropathy and tissue fibrosis. Mechanistically, this effect may be linked to silymarin-mediated suppression of NF- $\kappa$ B signaling and attenuation of oxidative stress, which in turn could lead to downstream regulation of miR-21 and miR-29 expression, ultimately reducing extracellular matrix accumulation and fibrotic remodeling. Other microRNAs, including miR-155, miR-146a, and the miR-221/222 cluster, may also be indirectly involved in the metabolic effects of silymarin. These actions are thought to occur primarily through modulation of inflammatory signaling pathways and endothelial function. However, the current evidence is largely indirect and predominantly derived from preclinical studies, and therefore requires further validation in clinical settings. Table 4 presents the predicted

microRNA-mediated regulatory network of *Silybum marianum* in T2DM.

### ***Citrullus colocynthis* (Bitter apple)**

#### **Phytochemical Profile and Bioactive Constituents**

*Citrullus colocynthis* (L.) Schrad., commonly known as bitter apple, colocynth, or desert gourd, is a perennial herbaceous plant belonging to the family Cucurbitaceae. It is a drought-tolerant desert species characterized by long, angular, creeping stems that spread extensively across the ground (117). The plant is distinguished by spherical fruits measuring approximately 5–10 cm in diameter, with a smooth, hard rind that changes from green with pale stripes to uniform yellow upon maturation. The fruit contains a spongy, white, intensely bitter pulp enclosing numerous flattened, ovoid seeds (117). From a pharmacognostic perspective, the medicinal material known as colocynth consists of the dried pulp of fully developed but unripe fruits after removal of the seeds. The remarkable pharmacological activity, as well as the well-recognized toxicity of the plant, is primarily attributed to highly bitter tetracyclic triterpenoids

known as cucurbitacins, particularly cucurbitacin E and cucurbitacin I glycosides. These compounds are responsible for the potent cathartic effects of the plant through intense irritation of the gastrointestinal mucosa (118, 119). In addition to cucurbitacins, *C. colocynthis* contains small amounts of alkaloids, flavonoids, phenolic compounds, and fixed oils rich in unsaturated fatty acids, particularly linoleic and oleic acids. Unlike cucurbitacins, these lipid constituents are considered non-toxic and, in certain regions, are used as edible oils (119). Although *C. colocynthis* has been used since antiquity as a traditional hypoglycemic remedy, modern pharmacological studies have also demonstrated its potential antidiabetic, hypolipidemic, cytotoxic, and anticancer properties (120, 121). Nevertheless, because cucurbitacins possess a considerably narrow therapeutic index, with excessive exposure capable of inducing severe gastrointestinal inflammation and potentially life-threatening systemic toxicity, the therapeutic application of *C. colocynthis* requires careful extract standardization and rigorous clinical safety evaluation.

**Table 4.** Predicted microRNA-mediated regulatory network of *Silybum marianum* in T2DM

| <b>microRNA</b>       | <b>Role in diabetic pathophysiology (in untreated state)</b>                         | <b>Proposed modulation by <i>Silybum marianum</i></b>                                                     | <b>Main signaling pathway</b>    |
|-----------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------|
| miR-146a              | Downregulated; contributes to sustained activation of NF-κB and chronic inflammation | Upregulation; restoration of this negative feedback regulator attenuates inflammatory signaling.          | NF-κB                            |
| miR-155               | Upregulated; promotes inflammatory cytokine production and insulin resistance        | Downregulation; reduction of inflammatory burden and partial preservation of insulin signaling integrity. | NF-κB/JAK-STAT/insulin signaling |
| miR-29 family (a/b/c) | Downregulated; associated with enhanced extracellular matrix deposition and fibrosis | Upregulation; suppression of ECM-related gene expression and attenuation of fibrotic remodeling           | TGF-β/Smad                       |

|             |                                                                                              |                                                                                                                        |                            |
|-------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------|
| miR-122     | Downregulated; linked to dysregulated lipid metabolism and hepatic steatosis                 | Normalization/upregulation; improvement of hepatic lipid homeostasis and reduction of steatosis                        | SREBP-1c/lipid metabolism  |
| miR-34a     | Upregulated; promotes $\beta$ -cell dysfunction, apoptosis, and cellular senescence          | Downregulation; enhanced cell survival through reduced p53-associated apoptotic signaling and increased Bcl-2 activity | p53/Bcl-2 apoptosis axis   |
| miR-221/222 | Upregulated; associated with vascular dysfunction and pathological angiogenesis              | Downregulation; suppression of abnormal endothelial proliferation and vascular remodeling                              | PI3K/Akt/MAPK              |
| miR-21      | Upregulated; promotes fibrosis, inflammation, and metabolic dysfunction via PTEN suppression | Downregulation; restoration of PTEN activity and inhibition of profibrotic signaling                                   | PTEN/PI3K/Akt/TGF- $\beta$ |

#### Pharmacological Mechanisms of *Citrullus colocynthis* in Diabetes Signaling

Available evidence suggests that *C. colocynthis* exerts multitarget antidiabetic effects through bioactive constituents, particularly cucurbitacins, acting on the pancreas, liver, and peripheral insulin-responsive tissues. Collectively, these mechanisms contribute to improved glucose homeostasis and glycemic control. The proposed miRNA-mediated mechanisms of *Citrullus colocynthis* are presented in Figure 1, illustrating its potential indirect effects on inflammatory, metabolic, oxidative stress,  $\beta$ -cell, and vascular regulatory networks. Within the pancreas, experimental studies have demonstrated that *C. colocynthis* extracts stimulate insulin secretion (120). This insulinotropic activity has been proposed to involve KATP channel-dependent signaling in pancreatic  $\beta$ -cells, leading to membrane depolarization, increased  $\text{Ca}^{2+}$  influx, and calcium-dependent exocytosis of insulin-containing granules. However, the precise molecular pathways remain incompletely characterized and require further investigation (121, 122). Concurrently, the potent antioxidant activity of *C. colocynthis* protects pancreatic  $\beta$ -cells against glucotoxicity- and lipotoxicity-induced oxidative stress, thereby supporting  $\beta$ -

cell survival and functional integrity. These cytoprotective effects appear to be mediated through enhancement of endogenous antioxidant defense systems, including increased activities of SOD, CAT, and GPx (123, 124). In peripheral tissues, constituents of *C. colocynthis* may alleviate insulin resistance through enhancement of insulin signaling, particularly via activation of the PI3K/Akt pathway. Activation of this signaling cascade promotes GLUT4 translocation to the plasma membrane in skeletal muscle and adipose tissue, thereby increasing peripheral glucose uptake and contributing to attenuation of postprandial hyperglycemia (125, 126). At the hepatic level, suppression of endogenous glucose production represents another important mechanism of action. Activation of AMPK inhibits key gluconeogenic regulators, including PGC-1 $\alpha$  and FOXO1, resulting in reduced expression of PEPCK and G6Pase, and consequently decreasing hepatic glucose output (127). In addition, inhibition of digestive enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase slows carbohydrate digestion and glucose absorption, thereby attenuating postprandial glycemic excursions. Furthermore, the anti-inflammatory properties of cucurbitacins, mediated through suppression of NF- $\kappa$ B signaling and reduced

production of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), may indirectly improve insulin sensitivity (128).

#### Epigenetic Modulation of *Citrullus colocynthis* Through microRNAs

Direct evidence regarding the epigenetic effects of whole *Citrullus colocynthis* extracts on microRNA expression in diabetes remains limited and fragmented. Nevertheless, based on available evidence concerning cucurbitacins, a hypothesis-driven framework can be proposed to explain the potential miRNA-mediated mechanisms underlying the antidiabetic effects of this medicinal plant. Since many miRNAs and signaling pathways targeted by cucurbitacins in cancer are also implicated in metabolic disorders, including DM, cautious extrapolation of these findings appears biologically plausible. Accordingly, cucurbitacins may improve insulin signaling by modulating miRNAs involved in insulin resistance and chronic inflammation, particularly miR-21 and miR-155. Downregulation of miR-21 may restore the expression of its target gene PTEN, thereby modulating the PI3K/Akt signaling pathway and improving insulin responsiveness (40). Likewise, suppression of miR-155, a key regulator of inflammatory signaling, may attenuate chronic inflammation and consequently enhance insulin sensitivity (74). In addition, activation of AMPK by *C. colocynthis* has been hypothesized to occur, at least in part, through inhibition of miR-451,

leading to derepression of its upstream kinase LKB1 and subsequent activation of AMPK signaling (129). Conversely, *C. colocynthis* may promote the expression of protective miRNAs involved in pancreatic  $\beta$ -cell homeostasis. Upregulation of the let-7 family (130), miR-7 (131), and miR-375 (34) could contribute to the preservation of  $\beta$ -cell survival, differentiation, and insulin secretory function under diabetic conditions. Furthermore, increased expression of the miR-29 family may represent an epigenetic mechanism through which cucurbitacins attenuate extracellular matrix deposition and tissue fibrosis, thereby slowing the progression of chronic diabetic complications (49). At the vascular level, modulation of miRNA networks may also contribute to the protective effects of *C. colocynthis*. Suppression of the miR-17–92 cluster (132), together with enhanced expression of the vasculoprotective miR-143/145 cluster (46, 47, 133), could potentially improve vascular homeostasis and mitigate the development of diabetic microvascular complications. Taken together, these proposed mechanisms are based primarily on indirect evidence derived from studies of purified cucurbitacins and related experimental models, rather than investigations using standardized *C. colocynthis* extracts in diabetes. Therefore, these hypotheses require validation through well-designed mechanistic studies integrating transcriptomic, epigenetic, and functional analyses. Table 5 presents the predicted microRNA-mediated regulatory network of *C. colocynthis* in T2DM.

**Table 5.** Predicted microRNA-mediated regulatory network of *Citrullus colocynthis* (bitter apple) in T2DM

| microRNA            | Role in diabetic pathophysiology (untreated state)                                                      | Proposed modulation by <i>Citrullus colocynthis</i>                                                                           | Main signaling pathway                                 |
|---------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| miR-143/145 cluster | Downregulated; associated with vascular smooth muscle phenotypic switching and diabetic atherosclerosis | Upregulation; potential restoration of vascular contractile phenotype and endothelial stability via anti-inflammatory effects | Vascular smooth muscle phenotype regulation            |
| miR-375             | Dysregulated; reduced expression contributes to $\beta$ -cell apoptosis and impaired insulin secretion  | Normalization; $\beta$ -cell protective effects may indirectly support physiological expression levels                        | $\beta$ -cell function/insulin exocytosis (MTPN, PDK1) |

|                       |                                                                                                            |                                                                                                                                                      |                                              |
|-----------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| miR-155               | Upregulated; promotes chronic inflammation and tissue injury                                               | Downregulation; likely mediated through suppression of NF- $\kappa$ B- and STAT3-associated inflammatory signaling by cucurbitacin-rich constituents | NF- $\kappa$ B/JAK-STAT                      |
| miR-29 family (a/b/c) | Downregulated; contributes to extracellular matrix accumulation and tissue fibrosis                        | Upregulation; potential antifibrotic effect via inhibition of profibrotic signaling cascades                                                         | TGF- $\beta$ /Smad/ECM regulation            |
| miR-21                | Upregulated; promotes fibrosis, inflammation, and insulin resistance via PTEN suppression                  | Downregulation; may restore PTEN activity and attenuate PI3K/Akt-driven profibrotic signaling                                                        | PTEN/PI3K/Akt                                |
| let-7 family          | Downregulated; associated with insulin resistance and increased inflammatory signaling                     | Upregulation; may contribute to improved insulin sensitivity and reduced inflammatory tone                                                           | Ras/IL-6 signaling/metabolic regulation      |
| miR-7                 | Downregulated; loss contributes to $\beta$ -cell dysfunction and impaired insulin secretion                | Upregulation; proposed $\beta$ -cell protective and insulin secretory support                                                                        | $\beta$ -cell identity and insulin secretion |
| miR-451               | Dysregulated under metabolic stress; associated with impaired AMPK activation                              | Downregulation; potentially relieves inhibition of the LKB1/AMPK axis, enhancing metabolic stress adaptation                                         | LKB1/AMPK                                    |
| miR-17-92 cluster     | Upregulated in proliferative diabetic complications; promotes angiogenesis and abnormal cell proliferation | Downregulation; may suppress pathological angiogenesis and proliferative signaling                                                                   | PI3K/Akt/angiogenesis pathways               |

### Concluding Remarks and Future Directions

Numerous studies have demonstrated that miRNAs play crucial biological roles in the pathogenesis, diagnosis, and management of various diseases. Due to their ability to regulate the expression of multiple target genes at the post-transcriptional level, miRNAs are involved in a wide range of cellular and molecular processes, including cell proliferation, differentiation, apoptosis, metabolism, and immune responses. Moreover, their remarkable stability in biological fluids and their disease-specific expression patterns have highlighted their potential as valuable and non-invasive biomarkers for the early detection, diagnosis, prognosis, and monitoring of various diseases. In addition to their diagnostic and prognostic applications, miRNAs have emerged as promising therapeutic targets, as modulation of

their expression may contribute to the prevention or treatment of disease-associated molecular abnormalities (134-136). The present review examined the molecular mechanisms underlying the antidiabetic effects of five medicinal plants widely used in traditional medicine (*Urtica*, *Eryngium*, *Cinnamomum*, *Silybum marianum*, and *Citrullus colocynthis*), with particular emphasis on the regulatory role of microRNAs (miRNAs). The findings of this conceptual review suggest that these medicinal plants may exert multitarget therapeutic effects by modulating a network of key miRNAs implicated in the pathophysiology of DM, particularly type 2 diabetes and its associated complications. Unlike conventional single-target pharmacotherapy, this network-oriented framework provides a plausible molecular explanation for the pleiotropic actions of

phytotherapeutic interventions in metabolic disease. One of the most notable observations is the convergence of different phytocomplexes on a limited set of miRNAs involved in inflammation, pancreatic  $\beta$ -cell survival, tissue fibrosis, and energy metabolism. In particular, miR-146a and miR-155, two central regulators of chronic inflammation, were repeatedly identified as potential regulatory nodes. Increased expression of miR-146a together with suppression of miR-155 may attenuate NF- $\kappa$ B and JAK/STAT signaling pathways, thereby reducing systemic inflammation and improving insulin sensitivity (137-139). Collectively, these findings suggest that the anti-inflammatory effects of medicinal plants may primarily involve epigenetic reprogramming through modulation of miRNA regulatory networks rather than direct inhibition of individual molecular targets. Therefore, a comprehensive understanding of miRNA-mediated mechanisms in metabolic inflammation may help overcome current translational barriers and provide a strong theoretical foundation for the development of novel diagnostic biomarkers and targeted therapeutic strategies for metabolic disorders, including T2DM. At the level of pancreatic  $\beta$ -cells, miRNAs such as miR-375, miR-7, and miR-30d are critical regulators of insulin secretion and  $\beta$ -cell survival. Experimental evidence indicates that silymarin and related phytocomplexes may enhance insulin secretion through modulation of  $\beta$ -cell signaling pathways, including KATP channel activity and PI3K/Akt activation (140-142). These effects support the hypothesis that phytochemicals may protect both peripheral insulin sensitivity and pancreatic  $\beta$ -cell integrity. Regarding chronic diabetic complications, the miR-29 family and miR-143/145 cluster emerged as key regulatory nodes associated with fibrosis and vascular dysfunction. Reduced miR-29 expression has been strongly linked to TGF- $\beta$ /Smad activation and extracellular matrix accumulation (143,

144). Among the studied plants, *Silybum marianum* is particularly notable, as it has been associated with antifibrotic and antioxidant effects that may indirectly restore miR-29 expression and reduce tissue fibrosis (116, 145). Similarly, modulation of miR-143/145 may contribute to vascular smooth muscle homeostasis and attenuation of atherosclerosis in diabetes (133, 146). In hepatic metabolism, miR-122 represents a central regulator of lipid and glucose homeostasis. Restoration of miR-122 expression has been associated with improved hepatic insulin sensitivity and reduced steatosis (147, 148). Silymarin, in particular, demonstrates strong hepatotropic activity, which may explain its prominent metabolic effects in diabetic models. Another important observation concerns context-dependent regulation of miRNAs such as miR-221/222. Rather than directly targeting miRNAs, phytochemicals may act upstream by reducing oxidative stress and inflammatory signaling, thereby indirectly normalizing aberrant miRNA expression in metabolic tissues (149). Oxidative stress and cellular senescence represent additional mechanistic axes in diabetes progression. The miRNAs, such as miR-34a and miR-200a, are involved in the suppression of antioxidant defenses and activation of pro-apoptotic pathways. Phytochemical-rich extracts may counteract these effects through activation of Nrf2 and SIRT1 signaling pathways (150, 151). Despite the conceptual coherence of this framework, most evidence remains indirect and derived from experimental models rather than clinical studies. In addition, variability in extract composition, dosage, and bioavailability limits direct translation to human disease.

## Conclusion

The medicinal plants *Urtica*, *Eryngium*, *Cinnamomum*, *Silybum marianum*, and *Citrullus colocynthis* exhibit significant therapeutic potential in DM. Current evidence suggests that these phytocomplexes may simultaneously

suppress pathogenic miRNAs, such as miR-155, miR-21, and miR-17-92, while restoring protective miRNAs including miR-146a, miR-29, miR-375, miR-143/145, and let-7 family members. Through coordinated modulation of these epigenetic regulators, medicinal plants may target multiple pathological processes, including chronic inflammation, insulin resistance,  $\beta$ -cell dysfunction, fibrosis, and vascular injury. This miRNA-centered framework bridges traditional phytotherapy with modern molecular medicine and supports the concept that multitarget botanical interventions may represent a rational therapeutic strategy for complex metabolic disorders, such as DM. However, these mechanisms remain largely hypothetical and require confirmation through rigorous mechanistic studies and well-designed clinical trials.

### Author Contributions

--- YY: Conceptualization, original draft writing, investigation, MM: Conceptualization, supervision, project administration, reviewing, and editing.

### Funding Statement

This study received no specific funding.

### Conflict of Interest

The authors declared no conflicts of interest.

### Acknowledgments

None

### Artificial Intelligence Statement

The authors used AI-assisted tools for English language editing, grammar improvement, and the initial design of the figure. The figure was subsequently further developed, reviewed, and approved.

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