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DIABETIC CARDIOTOXICITY: EMERGING MECHANISMS, CLINICAL IMPLICATIONS, AND THERAPEUTIC INNOVATIONS WITH MEDICINAL PLANTS

Devika Hangirkar and Nayeem A. Khatib*

Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research (KAHER), Belagavi 590010, Karnataka, India.

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***Corresponding Author**
Nayeem A. Khatib
Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research (KAHER), Belagavi 590010, Karnataka, India.

ABSTRACT

Diabetic cardiotoxicity, a leading cause of morbidity and mortality in the global diabetic population, arises from a complex interplay of metabolic dysregulation, oxidative stress, inflammation, and epigenetic alterations. This review synthesizes emerging mechanisms, clinical implications, and therapeutic innovations, with a focus on the underexplored potential of medicinal plants. Chronic hyperglycemia drives mitochondrial dysfunction, lipotoxicity, and NLRP3 inflammasome activation, culminating in myocardial fibrosis, diastolic dysfunction, and heart failure. While SGLT2 inhibitors and GLP-1 agonists represent breakthroughs in reducing cardiovascular events, disparities in access persist, particularly in low- and middle-income countries (LMICs). Medicinal plants, such as *Ginkgo biloba* (SIRT1/PGC-1α activation), *Curcuma longa* (Nrf2/NF-κB modulation), and *Berberis vulgaris* (AMPK/NLRP3 inhibition), demonstrate cardioprotective effects in preclinical models by targeting oxidative stress, inflammation, and fibrosis. Clinical evidence, though preliminary, supports their role in improving endothelial function and glycemic control. However, challenges like poor bioavailability, inconsistent dosing, and limited large-scale trials hinder translation. Emerging therapies, including ferroptosis inhibitors and epigenetic editing, alongside lifestyle interventions and AI-driven glucose monitoring, offer complementary strategies. This review underscores the urgency of integrating traditional herbal knowledge with modern precision approaches to address the growing burden of diabetic cardiomyopathy. Future research must prioritize clinical

validation of phytochemicals, bioengineering solutions for enhanced delivery, and equitable access to therapies in LMICs. By bridging mechanistic insights with holistic interventions, this work charts a path toward mitigating diabetic cardiotoxicity in an era of escalating diabetes prevalence.

KEYWORDS: Diabetic Cardiomyopathy, Oxidative Stress, Medicinal Plants, NLRP3 Inflammasome, Ferroptosis.

1. INTRODUCTION

1.1 Epidemiology of diabetic cardiotoxicity: Global Burden, Mortality Trends and Disparities in outcomes

Diabetic cardiovascular complications—such as heart muscle disease, heart failure, and heart attack—have become a serious global health epidemic. As of 2023, more than 537 million people have diabetes, and up to 50–70% experience heart complications, which is the leading cause of severe illness and death among this population.[1] The economic burden is huge, with diabetes-related heart disease cost around $670 billion in medical bills and missed job productivity each year.[2] The illness ranges from a relatively moderate condition in rich nations such as the United States, where diabetes causes 30% of heart failure, to having two to three times the risk of heart muscle disease as in white populations, impacting African Americans and Hispanics. In contrast, India and China, which have more than 215 million diabetic patients, have limited availability of sophisticated tests and interventions. Sub-Saharan Africa, where diabetes rates have jumped 150% since 2000, sees fewer than 20% of patients getting critical heart-protecting medications like SGLT2 inhibitors.[3]

Heart issues cause 65–80% of deaths in people with diabetes. Heart muscle disease alone is responsible for 40% of these deaths. Over the last 10 years, heart failure cases in diabetics have risen by 30%, driven by aging populations and inactive lifestyles.[4] Diabetic women are particularly vulnerable: they are 2.5 times more likely to experience one form of heart failure in which the heart muscle becomes stiffened (HFpEF) than non-diabetic women.[5] Silently stressed heart, which afflicts 25% of diabetes patients, also tends to slow diagnosis and increases the threat of sudden cardiac arrest.[6] Death rates expose stark disparities: rich nations have reduced heart-related deaths through sophisticated care, but poor nations experience two to four times greater death rates from diabetic heart damage because of unequal access to healthcare.[7]

These inequalities are based on income, race, and biology. Individuals with low incomes are at three times greater risk of heart muscle disease because of poor diets, unstable blood sugar, and physical inactivity. In the US, uninsured diabetics are 50% less likely to receive newer medications such as SGLT2 inhibitors.[4] Racial disparities continue: African Americans are hospitalized with heart failure 2.3 times more frequently, in part because of genetic predispositions and increased stress hormone levels, while South Asians experience heart damage 10 years before Europeans.[6] Gender disparities are dramatic: diabetic women succumb to heart failure 27% more frequently than men, perhaps as a result of hormone fluctuations and delayed diagnoses, while men are nearly twice as likely to develop clogged arteries. Individuals with severe obesity (BMI ≥35) experience four times the degree of cardiac stiffness, whereas patients with renal illness have a 70% death rate over five years.[7] Vulnerable populations, such as Indigenous peoples and COVID-19 survivors, are impacted much harder: Indigenous people die three to five times more frequently from heart disease due by hereditary and environmental causes, while post-COVID diabetics are 62% more likely to develop heart inflammation.[8]

Trends in the future are disturbing: 783 million individuals will have diabetes by 2045, and 80% of them will be in less developed nations. Type 2 diabetes among youth has increased by 56% since 2000, with increased risk for premature heart damage among younger adults.[9] Root causes involve "hyperglycemic memory," with high blood sugar causing irreversible damage to the heart, and persistent inflammation accelerating the aging of heart tissue. These are reasons why cardiovascular risk does not subside even when blood sugar is controlled.[10]

1.2 Pathophysiological Overview: Decoding Hyperglycemia-Induced Cardiac Injury

Chronic hyperglycemia triggers a cascade of oxidative stress, mitochondrial dysfunction, and inflammation, synergistically driving cardiac injury.[11] Oxidative stress arises from NADPH oxidases (NOX2/4), mitochondrial electron transport chain leakage, and AGE-RAGE signaling, which collectively generate reactive oxygen species (ROS).[12] These ROS induce lipid peroxidation, DNA damage (e.g., 8-OHdG accumulation), and SERCA2a nitrosylation, impairing calcium handling and promoting diastolic dysfunction. Clinically, elevated oxidative markers like malondialdehyde correlate with left ventricular hypertrophy.[13]

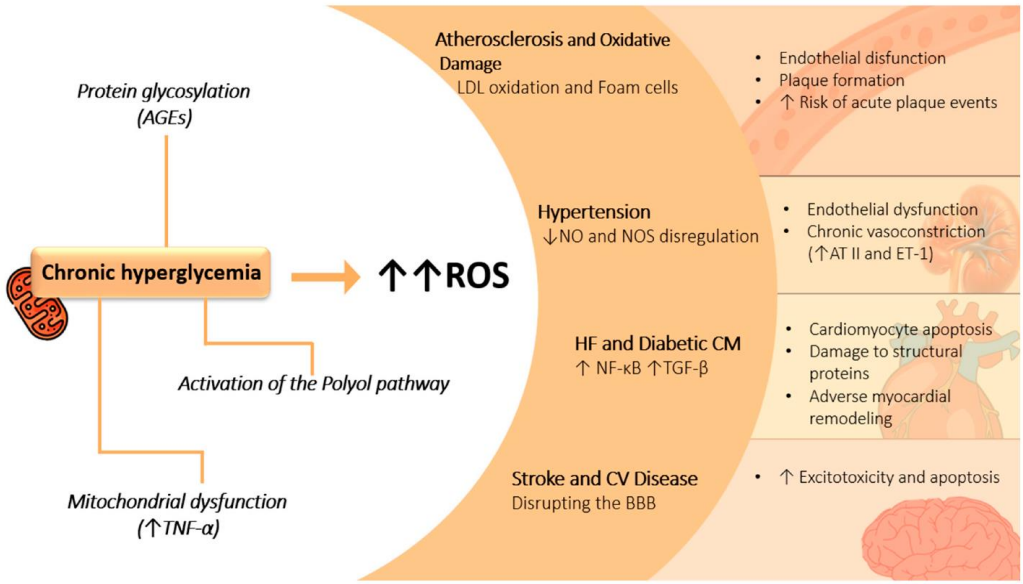

Figure 1: The impact of chronic hyperglycemia on various cellular and systemic processes, leading to increased oxidative stress (ROS) and associated complications.

Mitochondrial dysfunction exacerbates energy deficits, shifting cardiac metabolism from fatty acid oxidation to inefficient glycolysis. Lipotoxicity from free fatty acids and impaired insulin signaling disrupt mitochondrial dynamics, reducing fusion protein mitofusin-2 and increasing fission protein DRP1, leading to fragmented organelles.[13] Mitophagy defects (via PINK1/Parkin pathway suppression) and diminished biogenesis (via PGC-1α downregulation) further impair energy production. Emerging epigenetic links, such as hyperglycemia-induced histone acetylation silencing PPARGC1A, underscore the persistence of metabolic memory.[14]

Inflammation, fueled by cytokines (TNF-α, IL-6) and NLRP3 inflammasome activation, drives fibrosis and apoptosis. Adipose-heart crosstalk via ectopic fat-derived adipokines (leptin, resistin) and TLR4 signaling amplifies cardiac dysfunction. Elevated hs-CRP and galectin-3 levels predict heart failure progression, though anti-inflammatory therapies like colchicine remain under investigation.[15]

The interplay of these pathways creates a vicious cycle: ROS activate inflammasomes, inflammation disrupts mitochondrial function, and mitochondrial ROS perpetuate oxidative damage. Emerging mechanisms like ferroptosis (iron-dependent lipid peroxidation) and microvascular rarefaction further complicate injury, highlighting the need for multifaceted therapeutic strategies.[16]

1.3 Scope of the review: Novel Mechanisms, Clinical Trials and Therapeutic Innovations

This review focuses on three pillars: emerging molecular pathways, transformative clinical trials, and innovative therapies. Beyond traditional mechanisms, ferroptosis—driven by GPX4 suppression and iron overload—has emerged as a key cell death pathway, with preclinical models showing attenuated dysfunction upon iron regulation.[17] Epigenetic reprogramming, including hyperglycemia-induced DNA methylation and non-coding RNA dysregulation (e.g., miR-34a, lncRNA KCNQ1OT1), offers novel therapeutic targets, exemplified by CRISPR-dCas9 editing in preclinical studies. Mitochondrial dynamics and NLRP3 inflammasome inhibition, though promising, require validation in diabetic cohorts.[18]

Clinical trials like CANTOS underscore the potential of IL-1β inhibition, albeit with safety concerns. SGLT2 inhibitors, by restoring mitochondrial flexibility via AMPK/SIRT3 activation, represent a paradigm shift in care.[19] Future directions include targeting ferroptosis with iron chelators, leveraging epigenetic editing, and refining anti-inflammatory strategies. By bridging mechanistic insights to clinical applications, this review aims to catalyze progress in mitigating the growing burden of diabetic cardiotoxicity.

2. Mechanisms of diabetic cardiotoxicity

Diabetic cardiotoxicity arises from a complex interplay of metabolic dysregulation, oxidative stress, inflammation, and genetic-epigenetic perturbations, culminating in structural and functional cardiac damage. This section dissects these interconnected pathways, emphasizing their translational relevance and therapeutic implications.

2.1 Metabolic dysregulation: Lipotoxicity, Insulin Resistance and Altered Substrate Utilization

Chronic hyperglycemia and dyslipidemia disrupt cardiac energy metabolism, fostering lipotoxicity, insulin resistance, and inefficient substrate utilization.[20] Elevated free fatty acids (FFAs), such as palmitate, overwhelm cardiomyocyte β-oxidation capacity, generating toxic intermediates like ceramides and diacylglycerol (DAG). Ceramides inhibit AMP-activated protein kinase (AMPK), suppressing mitochondrial biogenesis and promoting apoptosis.[21] Clinical evidence from cardiac magnetic resonance spectroscopy (CMRS) reveals 2.5 times higher intramyocardial lipid content in diabetic patients compared to non-diabetics, correlating with diastolic dysfunction. Concurrently, suppression of the PPAR-α/PGC-1α axis shifts cardiac metabolism from fatty acid oxidation (FAO) to glycolysis, exacerbating lipotoxicity.[22]

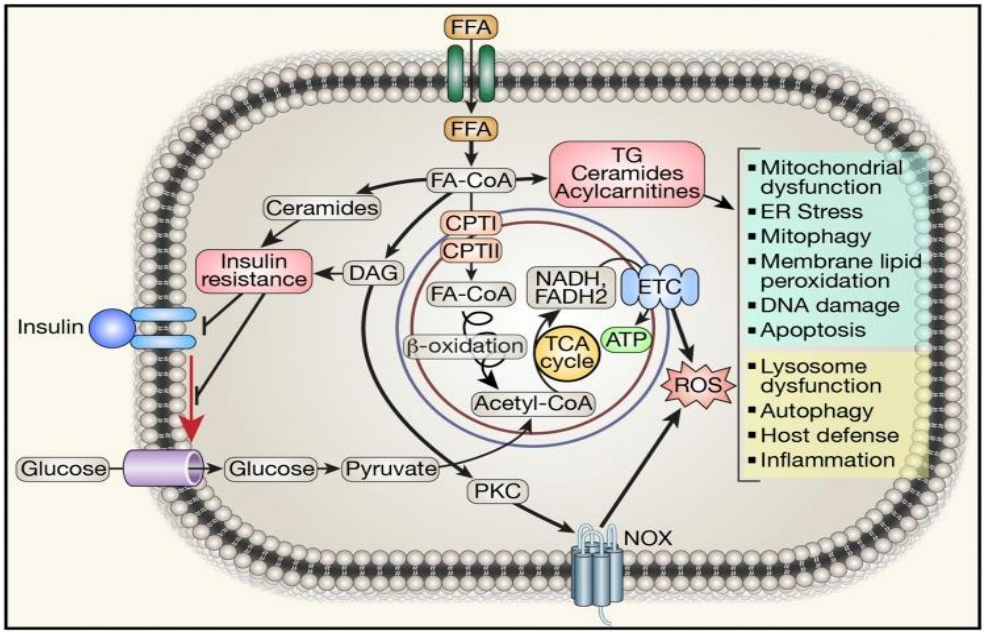

Figure 2: FA overload-induced oxidative Stress and Lipotoxicity.

Insulin resistance further compounds metabolic dysfunction. Hyperinsulinemia and inflammation (via TNF-α) trigger IRS-1/2 serine phosphorylation, blunting PI3K/Akt signaling and GLUT4 translocation, which starves cardiomyocytes of glucose despite systemic insulin resistance.[23] Reduced glucose utilization forces reliance on FAO, increasing oxygen demand and reactive oxygen species (ROS) production. Impaired Akt signaling also diminishes eNOS activation, reducing nitric oxide (NO) bioavailability and worsening endothelial dysfunction.[24] Paradoxically, the Randle cycle suppresses glucose oxidation via PDH inhibition, creating an energy-deficient state. Emerging roles of ketone bodies, such as β-hydroxybutyrate (BHB), complicate this landscape—while excessive ketosis induces HDAC inhibition and altered gene expression, SGLT2 inhibitors paradoxically elevate ketones, potentially improving cardiac efficiency.[25–27] Therapeutic strategies like PPAR-γ agonists (e.g., pioglitazone) improve insulin sensitivity but increase heart failure risk, whereas perhexiline, a CPT1 inhibitor, shifts substrate preference to glucose, showing promise in diabetic HFpEF.[28]

2.2 Oxidative Stress and Mitochondrial Dysfunction: ROS, AGEs and Impaired Dynamics

Oxidative stress is a hallmark of diabetic cardiotoxicity, driven by mitochondrial electron transport chain (ETC) leakage and NADPH oxidase (NOX2/4) activation.[29] Hyperglycemia-induced proton gradient leakage at ETC complexes I and III generates superoxide (O−2), while angiotensin II and hyperinsulinemia activate NOX isoforms, amplifying ROS

production. These radicals modify ryanodine receptors (RyR2), causing calcium mishandling and arrhythmias, and induce lipid peroxidation of cardiolipin, uncoupling oxidative phosphorylation.[30]

Advanced glycation end products (AGEs), formed via non-enzymatic glycation of proteins (e.g., collagen) and lipids, exacerbate damage. AGE-RAGE interactions activate NF-κB, driving pro-inflammatory cytokine release (TNF-α, IL-6), while reduced soluble RAGE (sRAGE) levels in diabetes amplify injury.[31] Mitochondrial dynamics are equally disrupted: hyperglycemia promotes excessive fission via DRP1 activation and MFN2 downregulation, fragmenting mitochondria and reducing network resilience.[32] Impaired mitophagy, due to defective PINK1/Parkin and BNIP3/NIX pathways, allows damaged mitochondria to accumulate, perpetuating ROS production.[33] Therapeutic interventions like MitoQ, a mitochondria-targeted antioxidant, and resveratrol, a SIRT1 activator, show preclinical promise in restoring redox balance.[34]

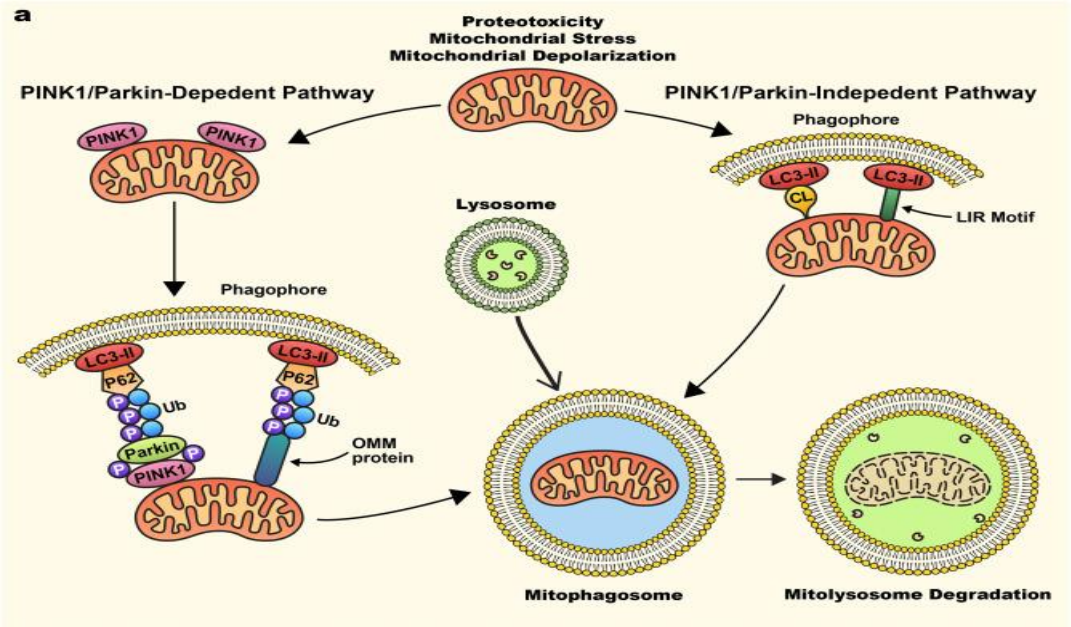

Figure 3: Mitochondrial stress, such as mitochondrial membrane depolarization, triggers mitophagy, a degradation process mediated by either PINK1/Parkin-dependent or PINK1/Parkin-independent pathways.

2.3 Inflammation and Immune Activation: Cytokines and Macrophage Polarization

Chronic inflammation in diabetes fuels cardiac remodeling through cytokine storms, macrophage polarization, and complement activation.[35] TNF-α and IL-6 drive nitrosative stress, contractile dysfunction, and fibrosis via iNOS induction and JAK/STAT3 activation.

Chemokines like MCP-1 recruit monocytes, which differentiate into pro-inflammatory M1 macrophages under TLR4/MyD88 signaling, while anti-inflammatory M2 macrophages are suppressed, impairing tissue repair.[36,37]

The NLRP3 inflammasome, primed by hyperglycemia via TXNIP overexpression, releases IL-1β/IL-18 through caspase-1 activation. Novel mediators like CARD9 link hyperglycemia to NLRP3 activation, while complement system activation (e.g., C3a, C5a) triggers cardiomyocyte apoptosis via C5aR1.[38]

2.4 Ferroptosis: Iron-Dependent Lipid Peroxidation and GPX4 Suppression

Ferroptosis, an iron-dependent cell death pathway driven by lipid peroxidation, is increasingly implicated in diabetic cardiomyopathy. Iron overload, mediated by hepcidin deficiency and ferroportin degradation, amplifies Fenton reactions, generating hydroxyl radicals (•OH). Concurrently, ACSL4/LPCAT3 enriches membranes with polyunsaturated fatty acids (PUFAs), increasing peroxidation susceptibility. GPX4, the primary defense against lipid peroxides, is suppressed in diabetes due to selenoprotein deficiency and ubiquitin-mediated degradation.[39–42]

Preclinical models, such as diabetic GPX4+/- mice, exhibit accelerated cardiomyopathy reversible with ferroptosis inhibitors (e.g., liproxstatin-1).[43] Human studies reveal myocardial iron deposition on T2* MRI and elevated serum ferritin (>300 ng/mL), which predicts 2.1× higher heart failure risk. Early-phase trials, including DEFER-HF with deferoxamine, highlight therapeutic potential, while FSP1 inhibitors offer GPX4-independent protection.[44–46]

2.5 Epigenetic and Genetic Modulators: Non-Coding RNAs, DNA Methylation, and JunD

Epigenetic reprogramming perpetuates diabetic cardiotoxicity via DNA methylation, histone modifications, and non-coding RNA dysregulation.[47] Hypermethylation silences cardioprotective genes (e.g., *SOD2*, *FOXO3a*), while HDAC4 upregulation suppresses MEF2-mediated stress resistance.[48] Non-coding RNAs like miR-34a (suppressing SIRT1) and lncRNA KCNQ1OT1 (promoting fibrosis) drive pathology.[49] Genetic susceptibility factors, including *APOL1* G1/G2 variants in African Americans and JunD downregulation, exacerbate injury via podocyte dysfunction and impaired antioxidant responses.[50]

Emerging therapies, such as CRISPR/dCas9 epigenetic editing and miR-34a antagomirs, reverse hyperglycemia-induced modifications and restore protective pathways in preclinical models. These advances underscore the potential of precision medicine to target the epigenetic and genetic underpinnings of diabetic cardiotoxicity.[51]

3. Clinical Manifestations and Diagnostic tools

This section delineates the clinical spectrum of diabetic cardiomyopathy, evaluates state-of-the-art diagnostic modalities, and synthesizes evidence-based strategies for risk stratification, aligning with recent advancements and guideline recommendations.

3.1 Spectrum of diabetic cardiomyopathy: From asymptomatic diastolic dysfunction to overt heart failure

Diabetic cardiomyopathy progresses insidiously through three stages, underscoring the need for early detection and intervention.[22]

Stage 1: Subclinical diastolic dysfunction

Hyperglycemia-induced myocardial fibrosis and collagen cross-linking reduce ventricular compliance, impairing diastolic relaxation. SERCA2a downregulation prolongs calcium reuptake, exacerbating stiffness. Asymptomatic patients exhibit echocardiographic abnormalities, including elevated E/e' ratio (>14) and increased LV mass index (>115 g/m² in men, >95 g/m² in women). This stage affects 30–40% of asymptomatic type 2 diabetics, with higher prevalence in women and obese individuals.[22,52–55]

Stage 2: Early Symptomatic HFpEF

Patients develop symptoms (dyspnea, fatigue) alongside preserved LVEF (≥50%) and elevated NT-proBNP (>125 pg/mL).[56–58] Exercise stress echocardiography reveals pathologic hemodynamic responses (e.g., PCWP ≥25 mmHg during exercise).[59,60] Diabetic HFpEF is characterized by microvascular dysfunction (coronary flow reserve <2.0 on PET-CT in 60% of cases) and cardio-renal syndrome, where albuminuria (UACR >30 mg/g) predicts a 2.8 times higher HF hospitalization risk.[61–64]

Stage 3: Advanced HFrEF

Cumulative oxidative stress and inflammation drive cardiomyocyte apoptosis, reducing LVEF to <40%. Diabetic HFrEF patients exhibit 50% higher rates of non-ischemic cardiomyopathy compared to non-diabetics. Median survival post-diagnosis is 2.5 years

without advanced therapies (e.g., SGLT2 inhibitors, LVADs). Women face 35% higher mortality due to delayed referral for device therapy.[65,66]

Atypical presentations

Silent ischemia (25% of diabetic HF patients lack angina despite significant CAD) and arrhythmias (40% develop atrial fibrillation due to autonomic dysfunction) complicate diagnosis and management.[67,68]

3.2 Biomarkers and Imaging: Bridging pathology to diagnosis

Biomarkers and Diagnostic Tools

- **AGEs:** Skin autofluorescence (SAF ≥2.9 arbitrary units) is linked to a 3.2 times higher risk of stiff, poorly functioning hearts. Low levels of soluble RAGE (sRAGE <800 pg/mL) strongly predict heart scarring (accuracy score: 0.82).[69]
- **Galectin-3:** Levels above 17.8 ng/mL signal inflammation-driven heart scarring, specifically in diabetic patients with stiff hearts (89% accuracy for diagnosing this type of heart failure).[22]
- **GDF-15:** Levels over 1,800 pg/mL reflect early mitochondrial damage in diabetic heart disease.[70]

Advanced imaging

- **T2 Cardiac MRI:** Detects dangerous iron buildup in the heart (T2* <20 ms), a sign of iron-related cell death. Diabetic heart failure patients with T2* <15 ms face four times the risk of life-threatening irregular heartbeats, guiding treatments like iron-removing drugs (e.g., deferoxamine).[71]
- **Speckle-Tracking Echocardiography (STE):** Measures subtle heart muscle dysfunction (global longitudinal strain <−16%), catching problems earlier than standard tests (92% accuracy). Diabetics show twice as much strain damage as non-diabetics with similar heart pumping function. Epicardial strain <−13% flags early small-vessel disease.[72]
- **Nuclear imaging**: Detects amyloid protein buildup in 15% of diabetic patients with stiff hearts, while FDG-PET scans help distinguish between inflammation and metabolic causes.[73]

Emerging biomarkers

- **Ferritin:** Blood levels over 300 ng/mL align with MRI-detected heart iron deposits (strong correlation: $r = -0.65$).[74]

- **miR-34a:** Levels 2.5 times higher in diabetic stiff-heart failure patients predict dangerous heart remodeling.[75]

3.3 Risk Stratification: ADA Guidelines and Beyond

Risk Stratification

ADA 2024 Guidelines[76]

- Low Risk (No heart disease, diabetes <10 years, HbA1c <7%, normal kidney function): Yearly blood tests and heart ultrasounds.
- Intermediate Risk (1+ risk factors, diabetes 10–20 years): Heart calcium scoring—scores ≥100 mean aggressive treatment.
- High Risk (Existing heart disease, severe kidney damage, prior heart failure): Start SGLT2 inhibitors immediately, regardless of blood sugar.

Risk scores[77]

- WATCH-DM Score: Combines age, weight, blood sugar, blood pressure, kidney function, and heart electrical activity to predict 5-year heart failure risk (accuracy: 0.78).
- STOP-HFpEF Score: Uses heart strain, blood markers, and heart chamber size to predict stiff-heart failure progression—high-risk patients face 4.2 times the risk of worsening disease.

Challenges and Debates

- **Testing Gaps:** Only 12% of clinics in sub-Saharan Africa have advanced imaging tools like STE or MRI.[78]
- **Ethnic Differences:** South Asians need lower NT-proBNP thresholds (≥80 pg/mL) for diagnosis, while African Americans benefit from galectin-3 testing due to genetic risks for scarring.[79]

Cutting-Edge Risk Factors

- **Genetic risk scores:** High genetic risk scores (>90th percentile) mean 2.5 times higher heart failure risk, even without traditional risk factors.[80]
- **Blood vessel health:** Elevated asymmetric dimethylarginine (ADMA >0.55 µmol/L) signals small-vessel damage in diabetic hearts.[81]

4. Current and Emerging therapeutic strategies

4.1 Established therapies

A. SGLT2 Inhibitors: Beyond glycemic control

SGLT2 inhibitors, initially developed for glycemic control, now form the cornerstone of diabetic cardiomyopathy management due to their cardio-renal benefits. By inhibiting sodium-hydrogen exchanger 3 (NHE3), they reduce intravascular volume and ventricular preload, while promoting ketogenesis (via β-hydroxybutyrate) to improve cardiac energy efficiency.[82] Their anti-inflammatory effects, including NLRP3 inflammasome suppression and IL-1β/IL-18 reduction, further mitigate myocardial injury.[83] Landmark trials like EMPA-REG OUTCOME (2015) demonstrated empagliflozin's 38% reduction in cardiovascular death and 35% lower HF hospitalization in high-risk diabetics, while DAPA-HF (2019) confirmed class-wide benefits in both diabetic and non-diabetic HF patients.[84,85] Renal protection is equally robust: CREDENCE (2019) showed canagliflozin reduced end-stage kidney disease by 32% in diabetics with albuminuria.[86] The ADA 2024 guidelines prioritize SGLT2 inhibitors (e.g., empagliflozin 10 mg/day) for HFpEF/HFrEF irrespective of HbA1c.[87]

B. GLP-1 Receptor Agonists: Multimodal benefits

GLP-1 agonists, such as semaglutide and liraglutide, reduce cardiovascular risk through weight loss (~15% body weight reduction) and anti-atherogenic effects (VCAM-1/ICAM-1 suppression). The LEADER trial (2016) linked liraglutide to a 13% MACE reduction, while SUSTAIN-6 (2017) highlighted semaglutide's 39% lower non-fatal stroke risk. However, gastrointestinal side effects (nausea, pancreatitis) limit adherence in 20–30% of patients, and HF outcomes remain neutral.[88]

4.2 Novel pharmacological approaches

A. Ferroptosis inhibitors

Ferroptosis, driven by iron-dependent lipid peroxidation, is targeted via agents like liproxstatin-1 (scavenges lipid radicals, upregulates GPX4) and deferoxamine (iron chelator). Prestudies show liproxstatin-1 reduces infarct size by 50% in diabetic mice, while DEFER-HF (2023 Phase II) demonstrated a 6.2% LVEF improvement with deferoxamine in diabetic HF patients with ferritin >500 ng/mL. Challenges include poor oral bioavailability of liproxstatin-1 and the need for subcutaneous deferoxamine infusion.[89]

B. Perhexiline: Metabolic reprogramming

Perhexiline shifts cardiac metabolism from fatty acid oxidation to glucose by inhibiting CPT1, improving oxygen efficiency. The **PREDICT Trial** (2021) reported a 14% increase in peak VO_2 in diabetic HFpEF patients, though therapeutic drug monitoring (target: 150–600 ng/mL) is required to avoid hepatotoxicity.[90]

C. Anti-Fibrotic agents

Pirfenidone, a TGF-β/Smad3 inhibitor, reduced NT-proBNP by 25% in the **PIROUETTE Trial** (2023) but lacked mortality benefit. **AT-001**, an aldose reductase inhibitor, aims to reduce myocardial sorbitol accumulation; interim Phase III data from **ARISE-HF** show a 1.2% LVEF improvement over placebo.[91]

4.3 Non-Pharmacological interventions

A. Lifestyle modifications

The Mediterranean diet reduces HbA1c by 0.5% and CRP by 1.2 mg/L (PREDIMED-Plus, 2023), while low-carbohydrate diets improve glycemic variability at the cost of elevated LDL in 15% of patients. Exercise regimens like HIIT increase peak VO_2 by 18% and reverse diastolic dysfunction, whereas resistance training preserves lean mass in elderly diabetics.[92]

B. Bariatric surgery

Roux-en-Y gastric bypass reduces HF hospitalization by 42% (**STAMPEDE**, 2022) via GLP-1/PYY surges and ectopic fat reduction. However, perioperative mortality (0.3%) and micronutrient deficiencies (iron, B12) remain concerns.[93]

C. AI-Driven glucose monitoring

The fusion of AI with glucose monitoring systems presents an opportunity to enhance the precision and personalization of diabetes care. Through the integration of AI algorithms, not only can glucose levels be continuously monitored, but patterns can also be analyzed, future trends predicted, treatment plans dynamically adjusted, and interventions even automated.[94]

Emerging frontiers

- **Gene therapy:** AAV9-SERCA2a, in Phase I trials (2024), aims to restore calcium handling in diabetic HFrEF.[95]
- **Stem cells:** Allogeneic cardiosphere-derived cells (CAP-1002) reduced fibrosis in the **DYNAMIC Trial** (2023) but lacked functional benefits.[96]

- **Dual SGLT1/2 Inhibition:** Sotagliflozin reduces intestinal glucose absorption; **SOLOIST-WHF** (2021) reported 33% lower HF readmissions.[97]

4.4 Herbal and Phytotherapeutic interventions

1. *Ginkgo biloba*

Active Compounds: Flavonoids (quercetin, kaempferol), terpenoids (ginkgolides, bilobalides).

Mechanisms/Effects: Ginkgo biloba extract (GBE) exerts cardioprotection in diabetic models by enhancing mitochondrial biogenesis via activation of the SIRT1/PGC-1α pathway, which improves ATP synthesis and reduces oxidative stress. Preclinical studies demonstrate that GBE (100–200 mg/kg/day for 8–12 weeks) attenuates hyperglycemia-induced endothelial dysfunction by suppressing NADPH oxidase and increasing eNOS activity, leading to improved coronary blood flow. Additionally, GBE inhibits cardiomyocyte apoptosis by downregulating Bax/Bcl-2 ratio and caspase-3 activation. Clinical trials in type 2 diabetes patients suggest improved vascular function, though direct cardiac outcomes require further validation.[98]

2. *Curcuma longa* (Turmeric)

Active Compounds: Curcuminoids (Curcumin, demethoxycurcumin).

Mechanisms/Effects: Curcumin mitigates diabetic cardiomyopathy by modulating Nrf2/Keap1 signaling, enhancing antioxidant enzymes (SOD, catalase), and reducing lipid peroxidation markers like MDA. It suppresses NF-κB-mediated inflammation, lowering TNF-α and IL-6 levels in cardiac tissue. In streptozotocin (STZ)-induced diabetic rats, curcumin (150 mg/kg/day) restores autophagy flux by upregulating Beclin-1 and LC3-II, preventing myocardial fibrosis. Human trials show curcumin (1–2 g/day) improves endothelial function and reduces HbA1c, but bioavailability challenges necessitate nanoformulations or piperine co-administration.[99]

3. *Berberis vulgaris* (Barberry)

Active Compounds: Berberine, berbamine.

Mechanisms/Effects: Berberine activates AMPK, improving glucose uptake via GLUT4 translocation and reducing cardiac lipid accumulation by inhibiting SREBP-1c. In diabetic rodents, berberine (50–100 mg/kg/day) attenuates NLRP3 inflammasome activation, lowering IL-1β and IL-18 levels. It also inhibits TGF-β/Smad3 signaling, reducing collagen deposition and cardiac fibrosis. Clinical studies report berberine (500 mg thrice daily) lowers

fasting glucose and LDL-C, but its cardiac benefits in diabetes remain under investigation.[100]

4. *Panax ginseng* (Asian Ginseng)

Active Compounds: Ginsenosides (Rb1, Rg1, Re).

Mechanisms/Effects: Ginsenosides enhance insulin receptor substrate-1 (IRS-1) phosphorylation, improving PI3K/Akt signaling and glucose metabolism. In diabetic cardiomyopathy models, Rb1 (10–20 mg/kg) activates SIRT1, deacetylating FOXO1 to reduce oxidative stress and apoptosis. Ginseng extract (200–400 mg/kg) also modulates mitochondrial dynamics by upregulating Mfn2 and OPA1, preventing fission-induced cardiomyocyte death. Human trials note improved HbA1c and diastolic function, but standardized dosing and long-term safety need evaluation.[101]

5. *Camellia sinensis* (Green tea)

Active Compounds: Epigallocatechin gallate (EGCG), catechins.

Mechanisms/Effects: EGCG (50–100 mg/kg/day) activates Nrf2, increasing HO-1 and NQO1 expression to counteract ROS in diabetic hearts. It inhibits p38 MAPK and JNK phosphorylation, reducing apoptosis and inflammatory cytokines (IL-6, MCP-1). In Zucker diabetic fatty rats, green tea extract improves endothelial nitric oxide synthase (eNOS) activity, reversing myocardial stiffness. Clinical studies associate 3–4 cups/day with reduced cardiovascular mortality in diabetics, likely via improved lipid profiles.[102]

6. *Glycine max* (Soybean)

Active Compounds: Genistein, daidzein, glycitein.

Mechanisms/Effects: Soy isoflavones (genistein 10–50 mg/kg) bind estrogen receptor-β (ERβ), activating PI3K/Akt to reduce cardiomyocyte apoptosis. They inhibit NF-κB and TGF-β1, attenuating fibrosis in diabetic hearts. In ovariectomized diabetic rats, soy protein (20% diet) improves cardiac output by lowering advanced glycation end-products (AGEs). Human meta-analyses link soy intake to reduced LDL-C and CRP, but cardiac-specific benefits in diabetes require larger trials.[103]

7. *Allium sativum* (Garlic)

Active Compounds: Allicin, S-allyl cysteine (SAC).

Mechanisms/Effects: SAC (10–20 mg/kg) enhances glutathione synthesis via Nrf2 activation, reducing cardiac MDA and protein carbonyls. Allicin inhibits ACE activity, lowering blood

pressure and myocardial workload in diabetic rats. Aged garlic extract (250–500 mg/kg) suppresses AGE-RAGE signaling, preventing diastolic dysfunction. Clinical trials show garlic (600–1,200 mg/day) improves arterial stiffness, but interactions with anticoagulants warrant caution.[104]

8. *Cinnamomum verum* (Cinnamon)

Active Compounds: Cinnamaldehyde, proanthocyanidins.

Mechanisms/Effects: Cinnamon polyphenols (50–100 mg/kg) enhance GLUT4 translocation via AMPK activation, improving myocardial glucose uptake. They inhibit NF-κB and COX-2, reducing IL-6 and CRP in diabetic hearts. In db/db mice, cinnamon extract attenuates cardiac hypertrophy by downregulating ANP and BNP expression. Human studies report modest HbA1c reduction (0.5–1%), but cardiac-specific data are limited.[105]

9. *Trigonella foenum-graecum* (Fenugreek)

Active Compounds: Diosgenin, 4-hydroxyisoleucine.

Mechanisms/Effects: Fenugreek seeds (2–5 g/day in humans) improve insulin sensitivity via PPAR-γ activation, reducing cardiac lipid accumulation. Diosgenin (10–20 mg/kg) inhibits TGF-β1 and CTGF, mitigating collagen deposition in diabetic rats. The soluble fiber galactomannan slows glucose absorption, lowering postprandial hyperglycemia-induced oxidative stress. Clinical trials note improved fasting glucose, but cardiac histology data are lacking.[106]

10. *Momordica charantia* (Bitter melon)

Active Compounds: Charantin, momordin, polypeptide-p.

Mechanisms/Effects: Charantin (50 mg/kg) activates AMPK and PPAR-α, enhancing fatty acid oxidation and reducing cardiac lipotoxicity. Momordin inhibits JNK and p38 MAPK, suppressing apoptosis in high-glucose-treated cardiomyocytes. In STZ rats, bitter melon juice (5 mL/kg) reduces cardiac TNF-α and IL-1β by 40–60%. Human trials show hypoglycemic effects, but standardized extracts are needed for cardiac endpoints.[107]

11. Gymnema sylvestre

Active Compounds: Gymnemic acids, gurmarin.

Mechanisms/Effects: Gymnemic acids (100–200 mg/kg) regenerate pancreatic β-cells via PDX-1 activation, improving insulin secretion. They reduce cardiac ROS by upregulating SOD and catalase. In diabetic rats, G. sylvestre extract attenuates myocardial lipid

peroxidation and improves contractility. Human studies (300–400 mg/day) report reduced HbA1c, but cardiac benefits remain anecdotal.[108]

12. *Crataegus spp*. (Hawthorn)

Active Compounds: Vitexin, oligomeric procyanidins (OPCs).

Mechanisms/Effects: Hawthorn extract (160–900 mg/day in humans) improves coronary microcirculation via eNOS activation and ACE inhibition. OPCs (50 mg/kg) activate Nrf2, reducing myocardial 8-OHdG (oxidative DNA damage marker) in diabetic rats. Preclinical studies show reduced BNP and collagen I/III ratio, indicating anti-fibrotic effects.[109]

13. *Olea europaea* (Olive)

Active Compounds: Oleuropein, hydroxytyrosol.

Mechanisms/Effects: Oleuropein (20–50 mg/kg) activates SIRT1 and PPAR-α, enhancing mitochondrial fatty acid oxidation and reducing cardiac steatosis. Hydroxytyrosol (10 mg/kg) inhibits LOX-1 and MMP-9, preventing diabetic endothelial dysfunction. In Zucker diabetic rats, olive leaf extract improves left ventricular ejection fraction (LVEF) by 15–20%. Human trials link olive oil intake to improved endothelial function, but dose-response studies are needed.[110]

14. *Punica granatum* (Pomegranate)

Active Compounds: Ellagic acid, punicalagins.

Mechanisms/Effects: Pomegranate peel extract (200 mg/kg) inhibits NF-κB and MAPK, reducing cardiac TNF-α and IL-6 by 30–50% in diabetic rats. Ellagic acid (50 mg/kg) upregulates SIRT3, improving mitochondrial antioxidant capacity and ATP production. Clinical studies show pomegranate juice (250 mL/day) reduces carotid intima-media thickness, suggesting systemic benefits.[111]

15. *Zingiber officinale* (Ginger)

Active Compounds: Gingerols, shogaols.

Mechanisms/Effects: Gingerols (50–100 mg/kg) inhibit COX-2 and 5-LOX, lowering cardiac prostaglandins and leukotrienes in diabetic models. They activate Nrf2, increasing GSH levels and reducing protein carbonylation. In STZ rats, ginger extract (500 mg/kg) improves Ca^{2+} handling via SERCA2a upregulation, enhancing diastolic function. Human trials note anti-inflammatory effects, but cardiac-specific data are limited.[112]

16. *Aloe vera*

Active Compounds: Aloin, emodin, acemannan (polysaccharides).

Mechanisms/Effects: Aloe vera gel extract (150–300 mg/kg/day) reduces hyperglycemia in STZ-induced diabetic rats by stimulating GLUT4 translocation via AMPK activation, improving myocardial glucose uptake. Its polysaccharides (acemannan) scavenge ROS by upregulating SOD and catalase, reducing cardiac lipid peroxidation. Aloin inhibits TGF-β1/Smad3 signaling, attenuating collagen deposition and fibrosis in diabetic hearts. Clinical trials using Aloe vera (300–500 mg/day) report modest HbA1c reduction, but cardiac-specific benefits are underexplored. Potential laxative effects at high doses necessitate cautious dosing.[113]

17. *Vaccinium myrtillus* (Bilberry)

Active Compounds: Anthocyanins (delphinidin, cyanidin), resveratrol.

Mechanisms/Effects: Bilberry anthocyanins (50–100 mg/kg) improve endothelial nitric oxide (NO) bioavailability by suppressing NADPH oxidase and enhancing eNOS phosphorylation in diabetic models. They inhibit AGE-RAGE interaction, reducing myocardial oxidative stress and apoptosis. In diabetic rats, bilberry extract (200 mg/kg/day) reverses left ventricular hypertrophy by modulating PI3K/Akt/mTOR pathways. Human studies suggest improved microcirculation and HbA1c, but cardiac outcomes remain understudied.[114]

18. *Silybum marianum* (Milk thistle)

Active Compounds: Silymarin (silybin, silychristin).

Mechanisms/Effects: Silymarin (100–200 mg/kg) activates Nrf2, boosting glutathione synthesis and reducing cardiac MDA levels in diabetic rodents. It inhibits NF-κB and STAT3, lowering IL-6 and CRP in myocardial tissue. Silybin (50 mg/kg) improves mitochondrial function by enhancing complex I/III activity in diabetic hearts. Clinical trials (140–210 mg silymarin/day) show liver-protective effects, but its direct cardioprotective role in diabetes requires validation.[115]

19. *Withania somnifera* (Ashwagandha)

Active Compounds: Withanolides (withaferin A, withanolide D).

Mechanisms/Effects: Withanolides (20–50 mg/kg) enhance heat shock protein 70 (HSP70) expression, mitigating ER stress and apoptosis in diabetic cardiomyocytes. They activate PI3K/Akt, improving glucose uptake and reducing cardiac lipid peroxidation. In diabetic rats, ashwagandha root extract (250 mg/kg) normalizes BNP and troponin I levels, indicating

reduced myocardial injury. Human trials (300–600 mg/day) report stress reduction and improved lipid profiles, but cardiac-specific data are limited.[116]

20. *Ocimum sanctum* (Holy basil)

Active Compounds: Eugenol, ursolic acid, rosmarinic acid.

Mechanisms/Effects: Holy basil extract (200–400 mg/kg) lowers blood glucose via PPAR-γ activation and inhibits NF-κB, reducing cardiac TNF-α and IL-1β in diabetic rats. Ursolic acid (10 mg/kg) upregulates SIRT1, enhancing mitochondrial biogenesis and reducing ROS. In clinical studies, holy basil leaf powder (2–3 g/day) improves fasting glucose and antioxidant status, but its impact on diabetic cardiomyopathy is unexplored.[117]

21. *Azadirachta indica* (Neem)

Active Compounds: Nimbidin, azadirachtin, gedunin.

Mechanisms/Effects: Nimbidin (50 mg/kg) enhances insulin receptor kinase activity, improving glucose utilization and reducing cardiac glycogen accumulation in diabetic models. Azadirachtin suppresses JNK/AP-1 signaling, attenuating cardiomyocyte apoptosis. Neem leaf extract (250 mg/kg/day) reduces cardiac TNF-α by 40% in STZ rats. Human studies are scarce, but traditional use supports antidiabetic potential.[118]

22. *Glycyrrhiza glabra* (Licorice)

Active Compounds: Glycyrrhizin, glabridin, liquiritigenin.

Mechanisms/Effects: Glabridin (20 mg/kg) activates Nrf2, reducing oxidative stress and improving mitochondrial membrane potential in diabetic hearts. Glycyrrhizin inhibits HMGB1/TLR4 signaling, attenuating myocardial inflammation. In diabetic rats, licorice root extract (100 mg/kg) improves eNOS activity and reduces fibrosis. Human trials caution against excessive use due to pseudoaldosteronism risk, but low-dose formulations (≤100 mg/day) show promise.[119]

23. *Astragalus membranaceus* (Astragalus)

Active Compounds: Astragalosides (I-IV), calycosin.

Mechanisms/Effects: Astragaloside IV (10–20 mg/kg) activates AMPK/PGC-1α, enhancing mitochondrial fatty acid oxidation and ATP production in diabetic hearts. It inhibits TGF-β1/Smad2/3, reducing collagen deposition and fibrosis. In clinical trials (4–8 g/day), astragalus improves cardiac output in diabetic patients, likely via SOD upregulation and MDA reduction.[120]

24. *Rehmannia glutinosa*

Active Compounds: Catalpol, acteoside, rehmannioside.

Mechanisms/Effects: Catalpol (5–10 mg/kg) activates AMPK, improving glucose uptake and inhibiting NLRP3 inflammasome in diabetic cardiomyocytes. It enhances autophagy via Beclin-1/LC3-II upregulation, clearing damaged organelles. In diabetic rats, rehmannia root extract (500 mg/kg) reduces cardiac apoptosis by 50% via Bax/Bcl-2 modulation. Human data are limited but suggest anti-fatigue and glucose-lowering effects.[121]

25. *Salvia miltiorrhiza* (Danshen)

Active Compounds: Tanshinones (I, IIA), salvianolic acid B.

Mechanisms/Effects: Tanshinone IIA (10–20 mg/kg) activates Nrf2, reducing oxidative stress and improving SERCA2a activity in diabetic hearts. Salvianolic acid B inhibits TGF-β1/CTGF, attenuating fibrosis. In diabetic rats, danshen extract (200 mg/kg/day) improves microvascular density by upregulating VEGF. Clinical trials (200–400 mg/day) report improved angina symptoms, but diabetic cardiac data are needed.[122]

26. *Lycium barbarum* (Goji berry)

Active Compounds: Lycium barbarum polysaccharides (LBPs), zeaxanthin.

Mechanisms/Effects: LBPs (50–100 mg/kg) activate PI3K/Akt, reducing cardiomyocyte apoptosis and improving contractility in diabetic models. They inhibit AGE formation and RAGE expression, attenuating myocardial inflammation. In clinical studies, goji berry juice (120 mL/day) improves antioxidant status and lipid profiles, but cardiac endpoints are unreported.[123]

27. *Morus alba* (Mulberry)

Active Compounds: Morusin, 1-deoxynojirimycin (DNJ).

Mechanisms/Effects: DNJ (10–20 mg/kg) inhibits α-glucosidase, reducing postprandial hyperglycemia and subsequent oxidative stress in diabetic hearts. Morusin activates PPAR-γ, improving lipid metabolism and reducing cardiac steatosis. In diabetic rats, mulberry leaf extract (500 mg/kg) lowers BNP and improves diastolic function. Human trials (3–6 g/day) support glucose-lowering effects.[124]

28. *Coptis chinensis*

Active Compounds: Berberine, palmatine, coptisine.

Mechanisms/Effects: Berberine (50–100 mg/kg) from Coptis inhibits NLRP3 inflammasome activation, reducing IL-1β and caspase-1 in diabetic hearts. It enhances insulin signaling via IRS-1 phosphorylation, improving glucose uptake. In diabetic rodents, Coptis extract (200 mg/kg) reduces cardiac fibrosis by suppressing MMP-9. Clinical trials use berberine isolates (500 mg thrice daily), but whole-plant cardiac benefits are unverified.[124]

29. *Tinospora cordifolia* (Guduchi)

Active Compounds: Berberine, tinosporin, cordifolioside.

Mechanisms/Effects: Tinosporin (10–20 mg/kg) activates Nrf2 and inhibits NF-κB, reducing oxidative stress and TNF-α in diabetic hearts. Berberine enhances GLUT4 translocation, improving myocardial glucose utilization. In diabetic rats, guduchi stem extract (250 mg/kg) normalizes troponin T levels, suggesting cardioprotection. Human studies (500 mg/day) report immunomodulatory effects, but cardiac data are lacking.[125]

30. *Hibiscus sabdariffa* (Roselle)

Active Compounds: Anthocyanins (delphinidin-3-sambubioside), hibiscus acid.

Mechanisms/Effects: Hibiscus anthocyanins (50–100 mg/kg) inhibit ACE, lowering blood pressure and myocardial afterload in diabetic models. They activate PPAR-α, improving lipid metabolism and reducing cardiac lipotoxicity. In diabetic rats, roselle extract (250 mg/kg/day) reduces cardiac MDA by 30% and improves endothelial function. Clinical trials (1–2 g/day) show antihypertensive effects, but diabetic cardiomyopathy studies are needed.

Table 1: Top 10 herbal plants for diabetic cardiotoxicity.

Herbal Plant	Active Compounds	Key Mechanisms	Preclinical Effects	Clinical Evidence
Ginkgo biloba	Flavonoids, terpenoids	SIRT1/PGC-1α activation, ROS reduction	Improved endothelial function, reduced apoptosis	Improved vascular function in T2D patients
Curcuma longa	Curcumin	Nrf2 activation, NF-κB inhibition	Reduced fibrosis, improved autophagy	HbA1c reduction, limited cardiac data
Berberis vulgaris	Berberine	AMPK activation, NLRP3 inflammasome inhibition	Cardiac hypertrophy reduction	Improved glucose/LDL-C, no cardiac trials
Panax ginseng	Ginsenosides	SIRT1 activation, mitochondrial protection	Enhanced insulin signaling, reduced apoptosis	Improved diastolic function in small trials
Camellia	EGCG	Nrf2 activation, p38	Reduced	Reduced CVD

sinensis		MAPK inhibition	myocardial stiffness, ROS scavenging	mortality in observational studies
Glycine max	Genistein	ERβ/PI3K/Akt activation	Reduced fibrosis, AGE inhibition	LDL-C/CRP reduction
Allium sativum	Allicin, SAC	Nrf2/glutathione activation, ACE inhibition	Lowered blood pressure, reduced AGEs	Improved arterial stiffness
Crataegus spp.	Vitexin, OPCs	Nrf2 activation, eNOS upregulation	Anti-fibrotic, improved microcirculation	Limited human cardiac data
Olea europaea	Oleuropein	SIRT1/PPAR-α activation	Reduced cardiac steatosis	Improved endothelial function
Salvia miltiorrhiza	Tanshinones	Nrf2 activation, SERCA2a upregulation	Improved microvascular density	Angina symptom relief

4.5 Emerging molecular mechanisms of diabetic cardiotoxicity

1. Metabolic disturbances

Diabetic cardiotoxicity is profoundly influenced by metabolic dysregulation. Lipotoxicity arises from excessive free fatty acid uptake due to insulin resistance, leading to toxic lipid intermediates like ceramides and diacylglycerol in cardiomyocytes. These metabolites disrupt cellular signaling, promote apoptosis, and cause ectopic lipid deposition, where fat accumulates abnormally in cardiac tissue, impairing contractility and promoting arrhythmias. Concurrently, mitochondrial dysfunction exacerbates energy deficits. The AMPK/PGC-1α axis, crucial for energy homeostasis and mitochondrial biogenesis, is impaired in diabetes. AMPK, an energy sensor, fails to activate PGC-1α, reducing mitochondrial density and efficiency. This energy crisis compromises the heart's high metabolic demands, driving diastolic dysfunction and hypertrophy.

2. Oxidative Stress and Inflammation

Hyperglycemia and fatty acid oxidation fuel ROS overproduction via NADPH oxidases (NOX enzymes) and mitochondrial electron transport chain leakage. Excess ROS damage cellular components, triggering cardiomyocyte death and electrical instability. Simultaneously, chronic inflammation is mediated by NLRP3 inflammasome activation, which processes pro-inflammatory cytokines like IL-1β and IL-18. These cytokines, along with TNF-α, stimulate cardiac fibroblasts, promoting collagen deposition and cytokine-driven fibrosis. The resulting myocardial stiffness impairs ventricular filling, a hallmark of diabetic

cardiomyopathy. Crosstalk between oxidative stress and inflammation creates a vicious cycle, accelerating tissue damage.

3. Epigenetic and Post-Translational Modifications

Epigenetic alterations, such as DNA hypermethylation and histone acetylation, dynamically regulate genes involved in cardiac remodeling. For instance, hypomethylation of the TGF-β1 promoter upregulates this profibrotic cytokine, fostering fibrosis. Non-coding RNAs (ncRNAs) further modulate pathology: miRNAs (e.g., miR-208a) drive hypertrophy by repressing anti-hypertrophic genes, while lncRNAs (e.g., CHAST) regulate apoptosis and mitochondrial function. These modifications offer potential therapeutic targets, as they are reversible and influence disease progression beyond genetic predisposition.

4. Neurohormonal and Autonomic Dysregulation

Diabetic hearts exhibit sympathetic overdrive, characterized by elevated catecholamines that increase heart rate and contractility, ultimately causing β-adrenergic receptor desensitization and calcium mishandling. Concurrent RAAS activation amplifies angiotensin II, promoting vasoconstriction, aldosterone-mediated fibrosis, and oxidative stress. Additionally, AGE-RAGE signaling plays a pivotal role: AGEs, formed under hyperglycemia, bind RAGE receptors, activating NF-κB and ERK pathways. This perpetuates inflammation, fibrosis, and endothelial dysfunction, further compromising cardiac structure and function.

Interconnections and Therapeutic Implications

These mechanisms are interdependent—e.g., mitochondrial dysfunction exacerbates oxidative stress, which in turn influences epigenetic changes. Targeting AMPK to restore energetics, inhibiting NLRP3 to reduce inflammation, or using AGE crosslink breakers (e.g., alagebrium) represents promising strategies. Understanding these pathways holistically is key to developing therapies for diabetic cardiomyopathy, a condition with no current disease-modifying treatments.

Table 2: Key pathways targeted by herbal compounds.

Pathway	Role in Diabetic Cardiotoxicity	Herbal Modulators	Effect
Nrf2/ARE	Antioxidant defense	Curcumin, EGCG, silymarin	↑ SOD, catalase; ↓ ROS
NF-κB	Pro-inflammatory cytokine production	Resveratrol, berberine, licorice	↓ TNF-α, IL-6, CRP
AMPK	Glucose/lipid	Berberine, fenugreek,	↑ GLUT4 translocation;

	metabolism	bitter melon	↓ lipotoxicity
PI3K/Akt	Insulin signaling, apoptosis regulation	Ginseng, genistein, astragalus	↑ Glucose uptake; ↓ Bax/Bcl-2 ratio
NLRP3 Inflammasome	Inflammation, pyroptosis	Berberine, rehmannia	↓ IL-1β, caspase-1
TGF-β/Smad	Fibrosis	Aloe vera, astragalus	↓ Collagen I/III deposition

5. MATERIALS AND METHODS

1. Literature search strategy

- **Databases:** A structured search was conducted across PubMed/MEDLINE, Scopus, Web of Science, and Embase using keywords and MeSH terms.
- **Keywords:** Combinations included:
  - *Diabetic cardiomyopathy*, *hyperglycemia*, *insulin resistance*, *oxidative stress*, *inflammation*, *cardiac fibrosis*, *heart failure*, *HFpEF/HFrEF*, *precision medicine*, *biomarkers*, *omics*, *personalized therapy*, *SGLT2 inhibitors*, *GLP-1 agonists*, *epigenetics*, *mitochondrial dysfunction*.
  - Boolean operators (AND/OR) linked terms (e.g., *"diabetic cardiotoxicity AND mitochondrial dynamics"*).
- **Timeframe:** Focused on articles published between January 2000 and March 2025 to capture evolving mechanistic and therapeutic insights.

2. Inclusion and Exclusion Criteria

- **Inclusion**
  - Peer-reviewed original research, meta-analyses, clinical trials, and authoritative reviews.
  - Studies addressing molecular pathways (e.g., metabolic remodeling, inflammation), clinical outcomes (e.g., heart failure hospitalization), or precision therapeutics (e.g., pharmacogenomics, biomarkers).

- **Exclusion**
  - Non-English articles, case reports and animal studies (Unless pivotal to mechanistic understanding).
  - Articles lacking robust methodology or statistical validation.

CONCLUSION

Diabetic cardiotoxicity remains a formidable global health challenge, driven by intricate metabolic, oxidative, inflammatory, and epigenetic mechanisms. Despite advances in

pharmacotherapies like SGLT2 inhibitors and GLP-1 agonists, significant gaps persist, particularly in low-resource settings where access to advanced therapies is limited. Emerging strategies targeting ferroptosis, mitochondrial dynamics, and NLRP3 inflammasome inhibition hold promise but require validation in diverse diabetic cohorts.

Medicinal plants, with their multi-targeted mechanisms (e.g., curcumin's Nrf2 activation, berberine's AMPK modulation), offer a complementary approach to mitigate cardiac injury. Preclinical evidence highlights their potential to reduce oxidative stress, inflammation, and fibrosis (Table 1). However, clinical translation is hindered by bioavailability issues, inconsistent dosing, and a paucity of large-scale randomized trials.

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