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Review Article

Potential Natural Products for the Treatment of Diabetic Cardiomyopathy: Advances and Outlooks

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Abstract

Diabetic cardiomyopathy (DCM), a diabetes-specific cardiovascular complication, is pathologically characterized by cardiomyocyte apoptosis, oxidative stress, inflammatory responses, and myocardial fibrosis, distinguishing it from other cardiac disorders, such as hypertension and coronary artery disease. Challenges in early diagnosis, coupled with the limited efficacy and adverse effects of current treatments, have made DCM a significant contributor to heart failure and mortality in patients with diabetes. Natural products, recognized for their diverse sources, structural variety, and multitarget therapeutic potential, have shown promise in preventing and treating DCM. Drawing on advances over the past five years, this review systematically summarizes the pharmacological effects and molecular mechanisms of natural products (e.g., flavonoids, terpenoids, phenylpropanoids, alkaloids, and polysaccharides) in the treatment of DCM, with the aim of providing a theoretical foundation for further research and drug development.

Introduction

In patients with diabetes, myocardial injury can be triggered by multiple metabolic and hemodynamic abnormalities, including chronic hyperglycemia, insulin resistance, dyslipidemia, hypertension, and obesity, either alone or in combination. These pathological factors collectively promote the transition of the myocardium from a normal state to one characterized by structural remodeling and functional decline, ultimately leading to diabetic cardiomyopathy (DCM). Epidemiological studies have reported that approximately 20% of patients with diabetes develop DCM, with the incidence substantially increasing among those with long-standing disease.[1] Amid the rising global prevalence of diabetes, the International Diabetes Federation projects a 46% increase in the number of people with diabetes worldwide by 2045, noting that such an increase is particularly rapid in developing countries, such as China and India.[2] This trajectory is expected to exacerbate the burden on individual health and national healthcare systems, further highlighting DCM as an urgent public health and clinical concern.

DCM is one of the most serious complications in patients with diabetes, with cardiovascular disorders representing the leading cause of heart failure and mortality in this population.[3,4] Pathologically, DCM is characterized by cardiomyocyte apoptosis, oxidative stress, and inflammatory activation. Clinically, it typically advances from early diastolic dysfunction, accompanied by myocardial fibrosis and hypertrophy, to ventricular dilation and reduced systolic function, eventually leading to overt heart failure.[5,6] The pathogenesis of DCM includes a multifactorial and interconnected network of mechanisms, including metabolic disturbances, insulin resistance, disrupted calcium homeostasis, mitochondrial dysfunction, oxidative stress, inflammatory activation, and ferroptosis (Fig. 1).[1,6–8] These pathways act independently or synergistically to promote disease onset and progression. DCM poses a substantial threat to patient survival and quality of life. Its early clinical presentation is usually subtle, typically manifesting only as mild diastolic impairment without specific symptomatic indicators. Furthermore, there are currently no validated biomarkers for early detection or risk stratification. Consequently, many patients are not diagnosed until the stage of established structural remodeling or overt cardiac dysfunction, thereby missing the optimal window for effective intervention.[9] In this pathological context, current clinical management focuses on controlling initiating factors and targeting central pathological pathways. Key strategies include stringent glycemic control, enhancement of myocardial energetics, and attenuation of oxidative stress and inflammatory responses. In glycemic manage-

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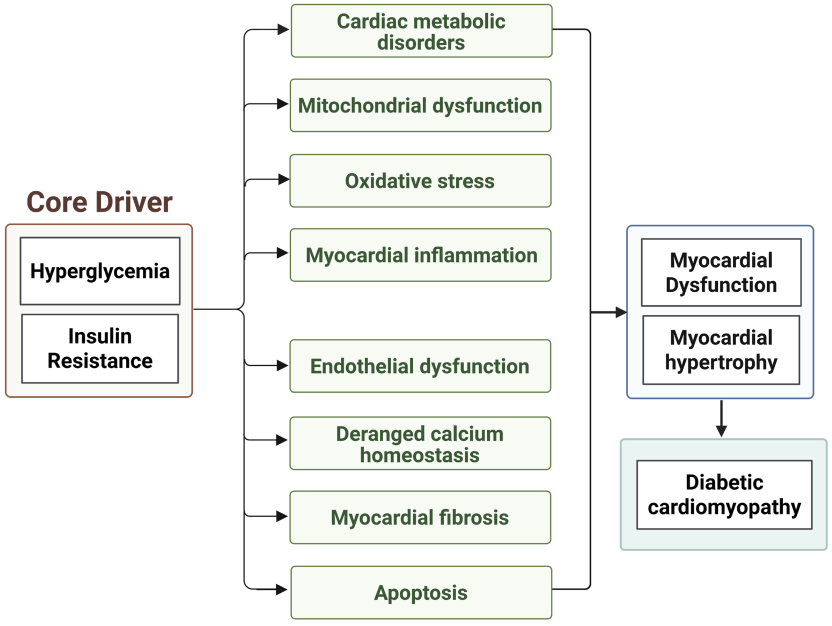

Fig. 1. The mechanisms of diabetic cardiomyopathy.

ment, metformin, a first-line agent, reduces direct glucose toxicity by enhancing insulin sensitivity in peripheral tissues and cardiomyocytes.[10] In contrast, sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, offer benefits beyond conventional treatments by regulating myocardial ketone metabolism to enhance energy supply and alleviate mitochondrial electron transport chain dysfunction, thereby introducing a mechanistically distinct therapeutic avenue for DCM.[11] Although current therapeutic approaches can slow disease progression to some extent, they face notable limitations. First, owing to the multifactorial pathogenesis of DCM involving interconnected pathways, such as glucotoxicity, oxidative stress, and myocardial fibrosis, existing interventions often fail to fully arrest or reverse the deterioration of myocardial structure and function. Second, several agents are limited by off-target complications. For example, SGLT2 inhibitors are associated with an increased risk of genitourinary tract infections, which may limit their clinical applicability.[11]

Natural medicines have a well-established historical foundation and considerable empirical basis for the management of diabetes and its complications. From ancient to present practices, traditional Chinese medicine (TCM) has accumulated extensive clinical experience in the regulation and treatment of "Xiaoke Disease" (the TCM equivalent of diabetes) and its associated cardiac manifestations. Classical TCM texts record numerous effective prescriptions and therapeutic approaches, providing valuable references for the treatment of diabetes-induced cardiac impairment. With the advancement of modern medical science, the identification of highly effective and low-toxicity monomeric compounds from natural products has emerged as an important strategy in contemporary drug discovery. Owing to their wide availability, structural diversity, and favorable safety profiles, natural medicines hold considerable potential for pharmaceutical development. Building on research advances over the past five years, this review systematically categorizes and elucidates the pharmacological effects and molecular mechanisms of various natural products, including flavonoids, terpenoids, phenylpropanoids, and alkaloids, against DCM (Figs. 2 and 3). By providing an in-depth analysis of the mechanisms through which these natural products exert therapeutic effects in DCM, this review aims to establish a solid theoretical foundation for subsequent basic research and drug development, thereby advancing the exploration of the considerable therapeutic potential of natural medicines in DCM and fostering progress in the field.

Materials and methods

PubMed, Web of Science, Elsevier ScienceDirect, China National Knowledge Internet, and the Wanfang Data Knowledge Service Platform were searched for the period 2021–2025 regarding the use of natural products to treat DCM using the following keywords: "natural products" or "natural monomeric compounds" or "flavonoids" or "terpenoids" or "phenylpropanoids" or "alkaloids" or "polysaccharides" and "diabetic cardiomyopathy" or "DCM."

Natural products for the treatment of DCM

Flavonoids

Flavonoids, defined by a characteristic C6–C3–C6 skeletal structure, are ubiquitously distributed throughout the plant kingdom. They are systematically classified into subcategories, such as flavonols, flavones, flavanols, and isoflavones, based on the oxidation state of the three-carbon bridge and the substitution pattern of the B-ring. The majority of flavonoids demonstrate a wide spectrum of biological activities, including antibacterial, antioxidant, and cardiovascular protective effects. Their protective role against DCM is distinguished by multitarget and multipathway mechanisms coupled with a favorable safety profile. The core protective mechanism involves modulation of key pathological processes in DCM, such as cardiac metabolism, insulin signaling, oxidative stress, inflammatory response, regulated cell death, myocardial

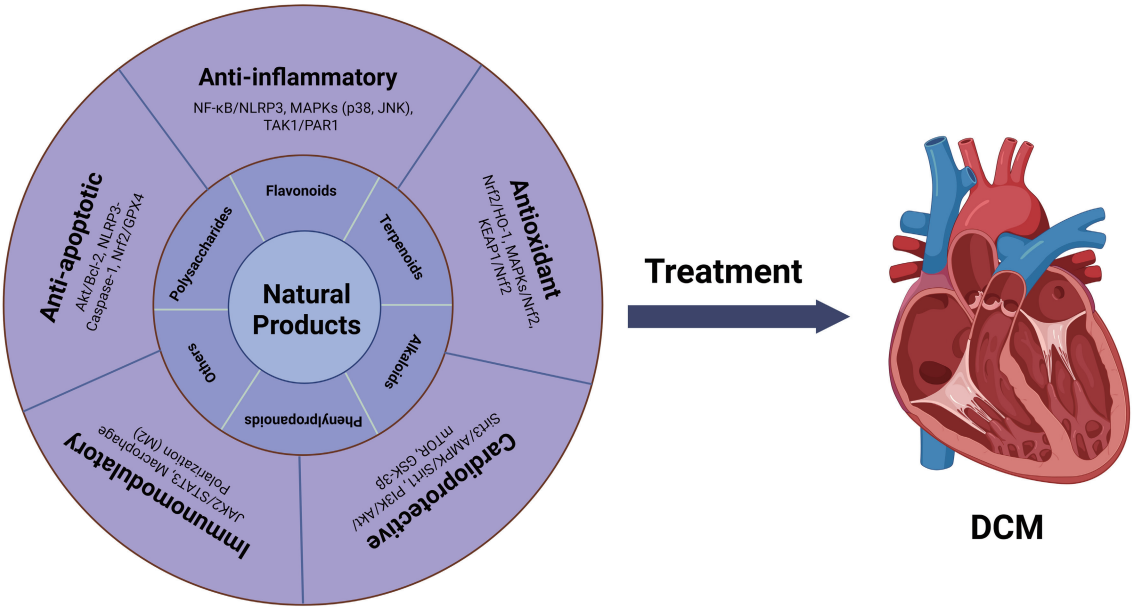

Fig. 2. Natural products and their biological activities against DCM. Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; Bcl-2, B-cell lymphoma-2; Caspase-3, cysteine-aspartic acid protease 3; DCM, diabetic cardiomyopathy; GPX4, glutathione peroxidase 4; GSK3β, glycogen synthase kinase 3 beta; HO-1, heme oxygenase 1; JAK2, Janus kinase 2; JNK, c-Jun N-terminal kinase; KEAP1, Kelch-like ECH-associated protein 1; MAPKs, Mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PAR1, protease-activated receptor 1; p38, p38 mitogen-activated protein kinase; PI3K, Phosphoinositide 3-Kinase; Sirt1, sirtuin 1; STAT3, signal transducer and activator of transcription 3; TAK, transforming growth factor-β-activated kinase 1.

fibrosis, and mitochondrial dysfunction.[12] In accordance with flavonoid subclassification, the following sections systematically discuss the pharmacological activities and underlying mechanisms of representative flavonoid monomers in DCM treatment. Table 1 summarizes the chemical profiles and mechanistic insights of flavonoids recently explored in DCM studies.

Flavonols

Flavonols, such as quercetin and icariin, alleviate pathological damage in DCM through multiple mechanisms. Quercetin ameliorates the pathological features of DCM through its anti-inflammatory, antioxidant, and antifibrotic activities. In murine DCM models, it attenuates myocardial inflammatory responses, enhances glycerophospholipid metabolism, and markedly mitigates myocardial injury, fibrosis, and inflammation.[13] Icariin, a bioactive compound derived from *Epimedium* species, exhibits anti-inflammatory and antioxidant properties, with a multifaceted action against DCM. Network pharmacology analyses revealed that icariin specifically targets myocardial fibrosis in DCM. Evaluation of its molecular interaction network has revealed a central role in regulating fibrosis-related signaling pathways.[14] In a type 2 diabetic rat model, icariin treatment markedly downregulated the expression of extracellular matrix proteins in cardiac tissues, reduced collagen deposition, and ameliorated myocardial remodeling.[15] Further mechanistic studies have reported that icariin enhances mitochondrial function and restores cardiomyocyte energy metabolism by activating the Apelin/Sirt3 signaling pathway, ultimately conferring protection against DCM.[16] Myricetin, a naturally occurring flavonol, mitigates cardiac dysfunction and myocardial fibrosis by modulating the gut microbiota and its metabolites and restoring intestinal barrier integrity, thereby preventing or attenuating DCM progression.[17] Sciadopitysin, a biflavonoid isolated from *Taxus* species, demonstrates potent anti-inflammatory and antioxidant activities. It protects cardiomyocytes from hyperglycemia-induced oxidative stress and apoptosis and alleviates DCM by activating the PI3K/Akt/GSK-3β signaling pathway.[18]

Flavones

In a DCM mouse model, baicalein enhances myocardial systolic function, attenuates oxidative stress and inflammatory responses, and alleviates cardiac injury and fibrosis. These protective effects are mediated by NF-κB/NLRP3 pathway suppression coupled with AKT and Nrf2 signaling pathway activation.[19] Baicalin exhibits efficacy in *in vivo* and *in vitro* models. It activates the SENP1/SIRT3 signaling axis, which inhibits cardiomyocyte overautophagy and aberrant cell death, diminishes oxidative stress, and restores mitochondrial function, collectively ameliorating DCM pathology.[20] In DCM rat models, galangin alleviates disease progression through multifaceted mechanisms, including modulation of hyperglycemia and hyperlipidemia as well as attenuation of myocardial oxidative stress, inflammatory responses, and apoptosis.[21] Astilbin and apigenin have also shown potential for DCM treatment. Although their exact mechanisms require further investigation, these compounds reveal promising therapeutic targets and enhance the evidence base for flavonoid-driven strategies for DCM treatment.[22]

Isoflavones

Puerarin, an isoflavone, ameliorates pathological damage in DCM by precisely targeting specific signaling pathways. Its protective effects against DCM are multimodal. Mechanistically, it upregulates caveolin-3 protein expression and suppresses the NF-κB and p38 MAPK pathways in H9C2 cardiomyocytes, thereby mitigating hyperglycemia- and hyperlipidemia-induced injury associated

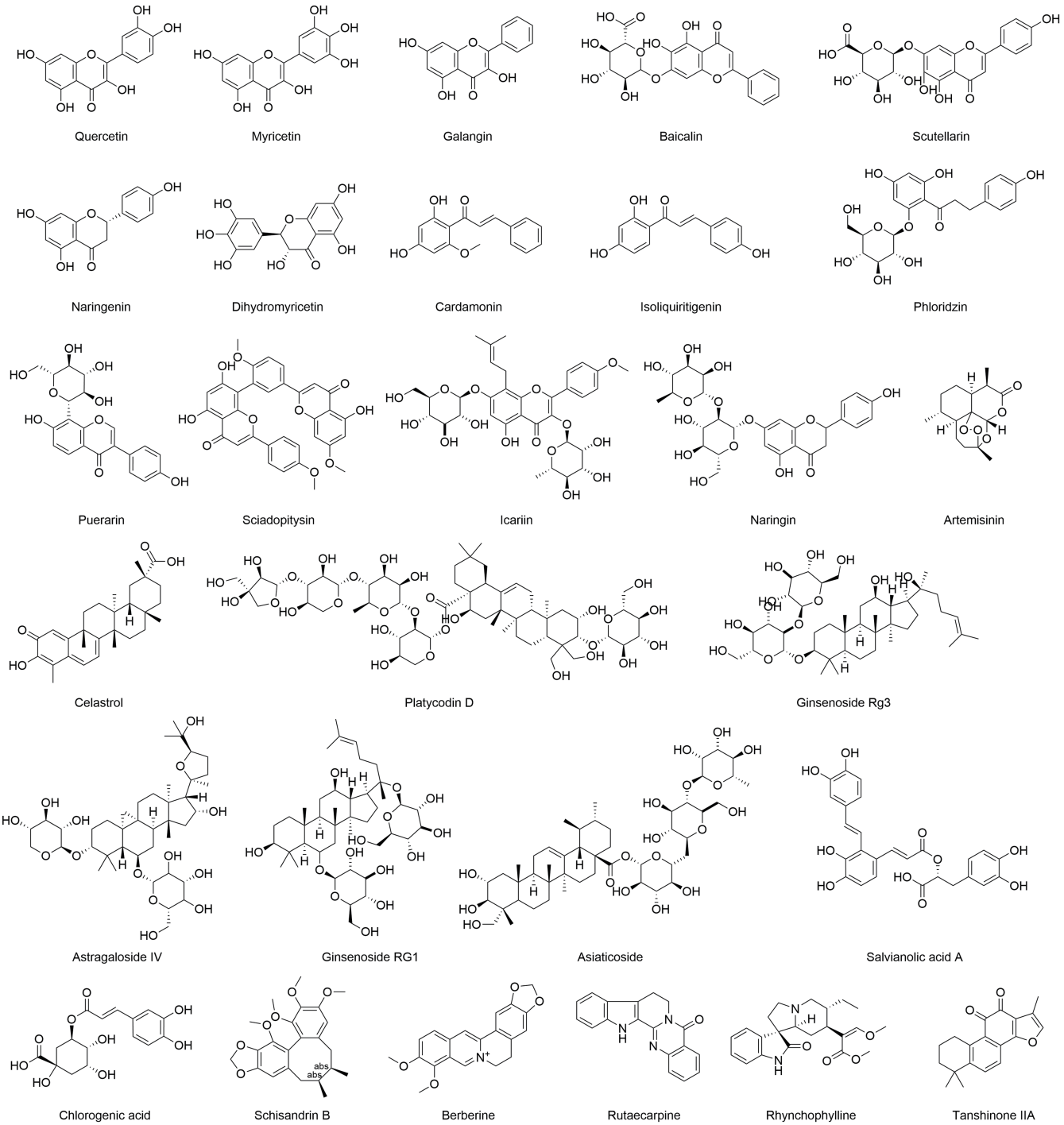

Fig. 3. Chemical structures of representative natural products for treating diabetic cardiomyopathy (DCM).

with inflammation, cellular hypertrophy, and apoptosis.[23] Moreover, puerarin inhibits the P2X7 receptor-mediated NLRP3–caspase-1–GSDMD pyroptosis axis, suppressing overactivation in cardiomyocytes and macrophages and interrupting the inflammatory cascade. In addition, it improves hyperglycemia-induced mitochondrial respiratory dysfunction in cardiomyocytes, collectively contributing to DCM alleviation.[24] Methylophiopogonanone A, a dihydroisoflavone, specifically inhibits the JNK1 signaling pathway. This suppression attenuates cardiomyocyte apoptosis and myocardial fibrosis, ultimately improving ventricular diastolic function in DCM rats.[25] Irisolidone mainly targets myocardial fibrosis. In a diabetic mouse model, it activates the adiponectin receptor 1–mediated AMPK pathway, inhibits collagen deposition, and downregulates the expression of collagen types I and III.

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Table 1. Representative natural products against DCM

No.	Classification	Compounds	Resources	Animal/Cell model	Target/Pathways/Mechanism	Effects	Evidence level[a]	Reference
1	Flavonoid	Quercetin	*Robinia pseudoacacia* L.	HFD+STZ-induced diabetic mice	Inhibition of inflammation and dysregulation of glycerophospholipid metabolism	Anti-inflammatory, antioxidant, cardioprotective	•	13
2	Flavonoid	Icariin	*Epimedium brevicornum* Maxim.	HFD+STZ-induced diabetic rats; HG-induced primary NRVMs	/	Anti-inflammatory, antioxidant	•••	14
				HFD+STZ-induced diabetic rats	Downregulation of extracellular matrix proteins in heart tissue	Anti-inflammatory, antioxidant		15
				Diabetic db/db mice; HG-induced primary NRVMs	Regulation of Apelin/Sirt3 signaling pathway	Anti-inflammatory, antioxidant		16
3	Flavonoid	Myricetin	*Myrica rubra* (Lour.) Sieb. et Zucc.	HFD+STZ-induced diabetic mice	Regulation of gut microbiota and their metabolites	Anti-inflammatory, antioxidant	•	17
4	Flavonoid	Sciadopitysin	*Taxus wallichiana* var. *chinensis* (Pilger) Florin	HG-induced AC16 cardiomyocytes	Activation of PI3K/Akt/GSK-3β signaling	Anti-inflammatory, antioxidant	•	18
5	Flavonoid	Scutellarin	*Scutellaria baicalensis* Georgi	STZ-induced diabetic mice	Activation of AKT and Nrf2/HO-1 signaling pathways; inhibition of NF-κB/NLRP3 signaling pathway	Anti-inflammatory, antioxidant	•	19
6	Flavonoid	Baicalin	*Scutellaria baicalensis* Georgi	HG-induced H9C2 cells; HFD-induced diabetic mice	Activation of the SENP1/SIRT3 pathway; Inhibition of autophagy and cell death	Anti-inflammatory, antioxidant	•	20
7	Flavonoid	Galangin	*Alpinia officinarum* Hance	STZ-induced diabetic rats	Modulation of oxidative stress, inflammation, and apoptosis	Anti-inflammatory, antioxidant	•	21
8	Flavonoid	Puerarin	*Pueraria montana* var. *lobata* (Ohwi) Maesen & S. M. Almeida	HGHL-induced H9C2 cells	Upregulation of CAV3 protein expression; inhibition of the NF-κB and p38MAPK pathways	Anti-inflammatory, antioxidant	••	23
				HG-induced H9C2 cells; LPS-induced RAW264.7 macrophages	Inhibition of P2X7R-mediated NLRP3-caspase-1-GSDMD pyroptosis pathway	Anti-inflammatory, antioxidant		24
9	Flavonoid	Methylophiopogonanone A	*Ophiopogon japonicus* (L.f.) Ker Gawl.	HFD+STZ-induced diabetic rats	Inhibition of JNK1 signaling	Anti-inflammatory, antioxidant	•	25
10	Flavonoid	Tectorigenin	*Belamcanda chinensis* (L.) Redouté	HFD+STZ-induced diabetic mice; Neonatal rat fibroblasts; HUVEC cell	Activation of the AdipoR1-mediated AMPK pathway	Anti-inflammatory, antioxidant, cardioprotective	•	26

(continued)

Table 1. *(continued)*

No.	Classification	Compounds	Resources	Animal/Cell model	Target/Pathways/Mechanism	Effects	Evidence level[a]	Reference
11	Flavonoid	Phlorizin	*Malus pumila* Mill., *Litchi chinensis* Sonn.	HFD+STZ-induced diabetic rats; HG-induced H9C2 cells	Inhibition of the MyD88/NF-κB signaling pathway; Modulation of the Nrf2/GPX4 axis	Anti-inflammatory, Hypoglycemic effect	•	27
12	Flavonoid	Cardamonin	*Alpinia katsumadai* Hayata	HFD+STZ-induced diabetic mice; HL-1/RAW264.7 cell	Activation of Nrf2 signaling via KEAP1 interaction	Anti-inflammatory, antioxidant	•	28
13	Flavonoid	Isoliquiritigenin	*Glycyrrhiza uralensis* Fisch.	HG-induced H9C2 cells	Modulation of the MAPKs/Nrf2 signaling pathway	Anti-inflammatory, antioxidant	•	29
14	Flavonoid	Dihydromyricetin	*Ampelopsis grossedentata* Hand.-Mazz.	STZ-induced diabetic mice; HG-induced primary NRVMs	Activation of SIRT3 signaling	Anti-inflammatory, antioxidant, cardioprotective	•	30
	Flavonoid	Dihydromyricetin	*Ampelopsis grossedentata* Hand.-Mazz.	HFD+STZ-induced diabetic rats; HG-induced primary NRVMs	Downregulation of miR-34a and thereby rescued autophagy	Anti-inflammatory, antioxidant, cardioprotective	•	31
15	Flavonoid	Naringenin	*Citrus aurantium* L., *Citrus maxima* (Burm.) Merr., *Citrus reticulata* Blanco	/	/	Anti-inflammatory, antioxidant, anti-diabetic	•	32
16	Flavonoid	Naringin	*Citrus ×paradisi* Macfad.	Diabetic db/db mice; Primary NRVMs	/	Anti-inflammatory, antioxidant, Hypoglycemic effect	•	33
17	Flavonoid	(−)-Epicatechin	*Theobroma cacao*	HGHL-induced H9C2 cell	Modulation of redox homeostasis, cell death, and autophagy	Anti-inflammatory, antioxidant	•	34
18	Terpenoid	Paeoniflorin	*Paeonia lactiflora* Pall.	STZ-induced diabetic mice	Modulation of gut microbiota and their metabolites	Anti-inflammatory, antioxidant, Cardioprotective	•	37
19	Terpenoid	Citronellal	*Cymbopogon citratus* (DC.) Stapf	HFD+STZ-induced diabetic rats	Inhibition of aberrant NHE1 activation	Anti-inflammatory, antioxidant	•	38
20	Terpenoid	Perillaldehyde	*Perilla frutescens* (L.) Britt.	STZ-induced diabetic rats; HG-induced H9C2 cells	Upregulation of miR-133a-3p, leading to GSK-3β inhibition	Anti-inflammatory, antioxidant	•	39
21	Terpenoid	β-Caryophyllene	*Citrus limon* (L.) Osbeck, *Cinnamomum cassia* (L.) D. Don, *Piper nigrum* L., *etc.*	HFD+STZ-induced diabetic mice	Modulation of the CB2R-dependent TLR4/NF-κB/MAPK signaling axis	Anti-inflammatory, antioxidant	•	41
22	Terpenoid	Artemisinin	*Artemisia annua* L.	HFD+STZ-induced diabetic rats	Modulation of the AGE-RAGE/HMGB-1 signaling pathway	Anti-inflammatory, antioxidant	•	44

(continued)

Table 1. *(continued)*

No.	Classification	Compounds	Resources	Animal/Cell model	Target/Pathways/Mechanism	Effects	Evidence level[a]	Reference
23	Terpenoid	Astragaloside IV	*Astragalus membranaceus* var. *mongholicus* (Bunge) P. K. Hsiao	HFD+STZ-induced diabetic rats; HGHL-induced H9C2 cells	Downregulation of CD36-mediated ferroptosis	Anti-inflammatory, antioxidant	••	47
				HFD+STZ-induced diabetic rats	Improvement of myocardial lipid metabolism	Anti-inflammatory, antioxidant, immunomodulatory		48
24	Terpenoid	Asiaticoside	*Centella asiatica* (L.) Urban	HFD+STZ-induced diabetic mice	Activation of the AMPK/Nrf2 pathway	Anti-inflammatory, antioxidant	•	49
25	Terpenoid	Platycodin D	*Platycodon grandiflorus* (Jacq.) A.DC.	HFD+STZ-induced diabetic mice; HGHL-induced H9C2 cells	Activation of AMPK signaling	Anti-inflammatory, antioxidant	•	50
26	Terpenoid	Celastrol	*Tripterygium wilfordii* Hook. f.	STZ-induced diabetic mice	Inhibition of the ACE/Ang II/AGTR1 signaling pathway	Anti-inflammatory	•	51
27	Terpenoid	Ginsenoside RG1	*Panax ginseng* C.A. Mey.	HG-induced primary NRVMs; STZ-induced diabetic mice	Secretion of exosomal circ-NOTCH1 and promotion of M2 macrophage polarization	Antioxidant, Cardioprotective	•	53
28	Terpenoid	Ginsenoside Rg3	*Panax ginseng* C.A. Mey.	Diabetic db/db mice; HL-induced 3T3-L1 and H9C2 cells	Activation of PPAR-γ and promotion of adiponectin signaling	Anti-inflammatory, antioxidant, Cardioprotective	•	54
29	Phenylpropanoid	Cinnamic acid	*Cinnamomum cassia* (L.) D. Don	HFD+STZ-induced diabetic rats	/	Anti-inflammatory, cardioprotective, anti-dyslipidemic and anti-diabetic	•	56
30	Phenylpropanoid	Chlorogenic acid	*Lonicera japonica* Thunb.	HG-induced H9C2 cells; HFD+STZ-induced diabetic rats	/	Alleviation of myocardial ER stress, anti-apoptotic	•	57
31	Phenylpropanoid	Ferulic acid	*Angelica sinensis* (Oliv.) Diels	HG-induced H9C2 cells; HFD+STZ-induced diabetic rats	Activation of the PACS2/IP3R2/FUNDC1/VDAC pathway	Anti-inflammatory, antioxidant, anti-apoptotic	•	58
				HFD+STZ-induced diabetic rats	Improvement of energy metabolism, reduction of lipotoxicity, modulation of inflammatory status, and restoration of ion homeostasis	Anti-inflammatory, antioxidant	•	59
32	Phenylpropanoid	Umbelliferone	*Ruta graveolens* L.	STZ-induced diabetic rats	Modulation of JAK/STAT signaling	Anti-inflammatory, antioxidant, anti-hyperglycemic, anti-hyperlipidemic	•	60

(continued)

Table 1. *(continued)*

No.	Classification	Compounds	Resources	Animal/Cell model	Target/Pathways/Mechanism	Effects	Evidence level[a]	Reference
33	Phenylpropanoid	Schisandrin B	*Schisandra chinensis* (Turcz.) Baill.	HG-induced H9C2 cells and primary NRVMs; STZ-induced diabetic mice; Diabetic db/db mice	Inhibition of the TAK1-MAPKs/NF-κB signaling pathway	Anti-inflammatory, antioxidant, cardioprotective	•	61
34	Phenylpropanoid	Salvianolic acid A	*Salvia miltiorrhiza* Bunge	HFD+STZ-induced diabetic rats	Activation of CRYAB signaling	Anti-inflammatory, antioxidant, anti-apoptotic	•	62
35	Phenylpropanoid	Salvianolic acid B	*Salvia miltiorrhiza* Bunge	HFD+STZ-induced diabetic mice	Inhibition of Smad7 ubiquitination	Antioxidant	••	63
				STZ-induced diabetic mice; HUVEC	Inhibition of IGFBP3 and promotion of angiogenesis	Antioxidant		64
36	Alkaloid	Rhynchophylline	*Uncaria rhynchophylla*(Miq.) Miq. ex Havil.	HFD+STZ-induced diabetic mice	Antagonism of RyR2 phosphorylation	Anti-inflammatory, antioxidant, antiarrhythmic	•	66
37	Alkaloid	Rutaecarpine	*Tetradium ruticarpum* (A. Juss.) T.G. Hartley	HG-induced H9C2 cells	Promotion of TRPV1-mediated autophagy	Cardioprotective, anti-inflammatory	•	67
38	Alkaloid	Berberine	*Coptis chinensis* Franch.	Diabetic db/db mice; HGHL-induced H9C2 cells	Modulation of SIRT3-mediated lipophagy and remodeling of lipid droplet homeostasis	Cardioprotective, anti-inflammatory, hypolipidemic	•••	68
				Diabetic db/db mice; HG-induced H9C2 cells	Regulation of mTOR/mtROS signaling leading to suppression of NLRP3 inflammasome activation	Anti-inflammatory, anti-diabetic		69
				HFD+STZ-induced diabetic rats; HG-induced H9C2 cells	Blockade of inflammasome activation and modulation of the miR-18a-3p/GSDMD pathway	Anti-inflammatory, anti-diabetic		70
39	Polysaccharide	Lentinan	*Lentinula edodes*	Diabetic db/db mice; HL-induced AC16 cells and HEK293T cells	Inhibition of CAV1/SDHA-regulated mitochondrial dysfunction	Antioxidant, hypolipidemic and hypoglycemic	•	71
40	Polysaccharide	Astragalus polysaccharide	*Astragalus membranaceus* (Fisch.) Bunge	HG-induced H9C2 cells; STZ-induced diabetic rats	Inhibition of BMP10-mediated signaling	Cardioprotective, antioxidant	•	72

(continued)

Table 1. *(continued)*

No.	Classification	Compounds	Resources	Animal/Cell model	Target/Pathways/Mechanism	Effects	Evidence level[a]	Reference
41	Polysaccharide	Polygonatum sibiricum polysaccharide	*Polygonatum sibiricum* Delar. ex Redoute	HFD+STZ-induced diabetic mice	Upregulation of cGMP-PKG signaling	Anti-inflammatory, antioxidant	•	73
42	Other	Curcumin	*Curcuma longa* L.	HFD+STZ-induced diabetic rats; HGHL-induced H9C2 cells	Modulation of Sirt1-Foxo1 and PI3K-Akt signaling pathways	Anti-inflammatory, antioxidant, anti-apoptotic	•	76
43	Other	Resveratrol	*Vitis vinifera* L.	HG-induced CMEC	Mediation of AMPK/Sirt1 signaling	Anti-inflammatory, antioxidant	•	80
44	Other	D-pinitol	*Glycine max* (L.) Merr.	STZ-induced diabetic mice	Modulation of the PI3K/Akt/mTOR pathway	Anti-inflammatory, antioxidant, cardioprotective, hypoglycemic	•	83
45	Other	Gastrodin	*Gastrodia elata* Blume	HFD+STZ-induced diabetic mice; HGHL-induced primary NRVMs	Inhibition of the KLK8-PAR1 signaling axis	Hypoglycemic	•	84
46	Other	Rhein	*Rheum palmatum* L.	HFD+STZ-induced diabetic mice; HG-induced primary NRVMs	Inhibition of mitochondrial dynamics disorder, apoptosis, and hypertrophy in cardiomyocytes	Anti-inflammatory, anti-fibrotic, hypoglycemic	•	86
47	Other	Tanshinone IIA	*Salvia miltiorrhiza* Bunge	HFD+STZ-induced diabetic mice; HG-induced NARCM cells	Modulation of SIRT1 and inhibition of endoplasmic reticulum stress in cardiomyocytes	Antioxidant, anti-diabetic	•	87
48	Other	Paeonol	*Paeonia suffruticosa* Andr.	STZ-induced diabetic rats; primary NRVMs	Modulation of the CK2α-Stat3 pathway and promotion of Opa1-mediated mitochondrial fusion	Anti-inflammatory, antioxidant	•	92
49	Other	6-Gingerol	*Zingiber officinale* Roscoe	HGHL-induced H9C2 cells; HFD+STZ-induced diabetic mice	Activation of Nrf2/HO-1 signaling	Anti-inflammatory, antioxidant, anti-apoptotic	•	93

[a]Evidence levels are indicated by the number of dots, which correspond to the quantity of published articles reporting the compound: •, one study; ••, two studies; •••, three or more studies. AdipoR1, adiponectin receptor 1; AGE-RAGE, advanced glycation end products-receptor for advanced glycation end products; AKT, protein kinase B; AMPK, mitogen-activated protein kinase; BMP10, bone morphogenetic protein 10; CAV1, caveolin 1; CAV3, caveolin 3; CB2R, cannabinoid receptor type 2; CD36, cluster of differentiation 36; CK2α, casein kinase II alpha; CRYAB, crystallin alpha B; cGMP-PKG, cyclic guanosine monophosphate/protein kinase G; GPX4, glutathione peroxidase 4; GSDMD, Gasdermin D; HG, high glucose ; HGHL, high glucose and high lipid; HFD, High-Fat Diet; HL, high lipid; HMGB-1, high mobility group box 1; HO-1, heme oxygenase 1; IGFBP3, insulin-like growth factor binding protein 3; JNK1, c-Jun N-terminal kinase 1; KEAP1, Kelch-like ECH-associated protein 1; KLK8, kallikrein related peptidase 8; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; mtROS, mitochondrial reactive oxygen species; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain; Opa1, mitochondrial dynamin like GTPase; p38MAPK, p38 mitogen-activated protein kinase; P2X7R, purinergic receptor P2X 7; PAR1, protease-activated receptor 1; PI3K, phosphoinositide 3-kinase; RyR2, ryanodine receptor 2; SDHA, succinate dehydrogenase complex flavoprotein subunit A; SENP1, Sentrin/SUMO-specific protease 1; SIRT1, sirtuin 1; Smad7, SMAD family member 7; STAT3, signal transducer and activator of transcription 3; STZ, streptozotocin; TLR4, Toll-like receptor 4; TRPV1, Transient receptor potential cation channel subfamily V member 1.

These effects alleviate cardiac fibrosis and help preserve myocardial structural and functional homeostasis.[26]

Chalcones

Chalcones, a unique flavonoid subclass characterized by an unsaturated ketone structure in the central three-carbon chain, demonstrate protective properties against DCM that are closely associated with their distinctive molecular architecture. Phlorizin, present in various fruits and vegetables, exerts anti-inflammatory and antioxidant effects. It alleviates myocardial inflammation by inhibiting the MyD88/NF-κB pathway, attenuates oxidative stress and ferroptosis by modulating the Nrf2/GPX4 axis, and improves DCM by regulating glycerophospholipid metabolism. These synergistic multipathway actions contribute to cardiac function preservation.[27] Cardamonin activates the Nrf2 antioxidant signaling pathway in macrophages by binding to the Kelch domain of KEAP1, thereby attenuating cardiomyocyte injury induced by M1-polarized macrophages.[28] Isoliquiritigenin mitigates hyperglycemia-induced myocardial damage in DCM through a dual mechanism. Furthermore, it suppresses inflammatory responses, including IL-6 reduction and TNF-α release, by inhibiting MAPKs and alleviates oxidative stress through Nrf2 activation, decreasing ROS and MDA levels. Evidence from *in vitro* and *in vivo* studies supports isoliquiritigenin as a promising therapeutic candidate for DCM.[29]

Other categories

Dihydromyricetin demonstrates free radical scavenging, antioxidant, and anti-inflammatory properties. It confers protection against DCM through dual regulatory mechanisms. First, it activates sirtuin 3, thereby suppressing oxidative stress, inflammation, and necroptosis and ameliorating cardiac dysfunction, myocardial hypertrophy, and fibrosis.[30] Second, it downregulates miR-34a to promote autophagy, alleviating hyperglycemia-induced cardiomyocyte injury.[31] Naringenin and naringin mainly counteract oxidative stress in DCM, with their protective effects confirmed experimentally. Specifically, naringenin modulates key oxidative stress signaling pathways in DCM. By modulating these pathways, naringenin helps prevent ROS-mediated damage, making it a promising therapeutic candidate, as specifically highlighted in recent reviews on antioxidant therapies for DCM.[32] In a type 2 diabetic mouse model, naringin directly acts on cardiomyocytes, enhancing hyperglycemia-induced metabolic dysregulation, reducing apoptosis, and maintaining normal cellular function, thereby providing experimental support for its cardioprotective role in DCM.[33] The protective effect of (−)-epicatechin against DCM is attributed to its intrinsic activity and the contribution of its colonic metabolite, 2,3-dihydroxybenzoic acid. When administered alone or in combination with metformin, they synergistically regulate cardiomyocyte redox homeostasis, inhibit aberrant apoptosis, and modulate autophagy, effectively counteracting hyperglycemia- and hyperlipidemia-induced cardiomyocyte damage.[34] Anthocyanins mainly target the prevention and control of myocardial fibrosis. By specifically inhibiting the IL-17 signaling pathway, they attenuate the inflammatory activation of cardiac fibroblasts and collagen synthesis under high-glucose conditions, thereby preserving cardiac structural integrity and contractile function. These findings offer direct experimental evidence for the targeted intervention of myocardial fibrosis in DCM.[35]

Flavonoids exert cardioprotective effects against DCM through multitarget interventions that synergistically regulate core pathological processes, primarily via four interconnected mechanisms: alleviating myocardial oxidative stress by activating pathways such as Nrf2 or directly scavenging ROS; broadly inhibiting classical inflammatory cascades, including NF-κB and NLRP3; modulating signaling pathways such as AMPK and TGF-β to reduce collagen deposition and counteract myocardial fibrosis and remodeling; and maintaining cardiomyocyte viability and function by restoring SIRT3 activity, improving mitochondrial metabolism, and inhibiting diverse cell death pathways such as apoptosis and pyroptosis. Collectively, while different flavonoid subclasses exhibit distinct emphases, they embody the inherent advantage of natural compounds in "multi-pathway synergistic regulation," offering a compelling scientific rationale for integrated therapeutic strategies in DCM.

Terpenoids

Terpenoids are among the largest and most structurally diverse families of natural products, derived from a wide range of organisms, such as higher plants, fungi, microorganisms, and marine species. Their carbon skeletons comprise isoprene (C5H8) units connected in head-to-tail or tail-to-tail configurations. Terpenoids are systematically categorized into monoterpenes, sesquiterpenes, diterpenes, triterpenes, and polyterpenes according to the number of their isoprene units. This structural diversity is the foundation for their broad biological activities and substantial pharmacological potential, encompassing anti-inflammatory, antioxidant, metabolic-regulating, and cytoprotective effects, as outlined in key reviews.[36] Current studies have reported that terpenoids can modulate key pathological processes in DCM through multitarget and multipathway mechanisms. They hold promising potential for improving cardiac function, attenuating myocardial injury, and delaying disease progression, highlighting their value as a source of novel natural therapeutics against DCM. The following sections discuss these findings, organized by terpenoid subclass and supported by notable recent studies.

Monoterpenes

Monoterpenoids, an important class of structurally diverse natural products with a broad spectrum of bioactivities, have shown considerable potential in mitigating the pathological progression of DCM. Current research indicates that various monoterpenoid compounds can exert therapeutic effects by targeting key pathological processes involved in DCM. For example, paeoniflorin ameliorates cardiac dysfunction in DCM mice by modulating the composition and structure of the gut microbiota, optimizing intestinal microecological balance, and regulating microbial metabolite production. These adaptations confer resistance to ferroptosis in cardiomyocytes, alleviating myocardial injury and oxidative stress.[37] In a DCM rat model, citronellal has shown therapeutic potential. Although its precise mechanism remains unclear, existing evidence suggests that its cardioprotective effects involve inhibition of aberrant sodium-hydrogen exchanger 1 activation. This insight lays the groundwork for further exploration of its therapeutic targets and molecular pathways, supporting its potential as a monoterpenoid candidate for DCM treatment.[38] Perillaldehyde exerts protective effects against DCM by modulating noncoding RNA-mediated signaling. Specifically, it upregulates myocardial miR-133a-3p expression, which in turn suppresses GSK-3β activity, ultimately alleviating cardiomyocyte hyperproliferation, apoptosis, and fibrosis in DCM.[39]

Sesquiterpenoids

Sesquiterpenoids are characterized by potent anti-inflammatory

and antioxidant activities, which contribute to their substantial cardioprotective efficacy against DCM. Patchouli alcohol alleviates DCM-induced myocardial injury, fibrosis, and inflammation by modulating the JAK2/STAT3 signaling pathway.[40] β-Caryophyllene activates the type 2 cannabinoid receptor, thereby alleviating DCM in mice by suppressing oxidative stress and inflammatory responses.[41] β-Elemene attenuates hyperglycemia-induced myocardial inflammation and remodeling by inhibiting JAK/STAT3- and NF-κB-mediated inflammatory pathways, thereby preventing diabetes-induced cardiac injury.[42] Costunolide ameliorates cardiac injury and dysfunction in diabetic mice through dual mechanisms: suppression of NF-κB-driven inflammation and activation of Nrf-2-mediated antioxidant defense.[43] Similarly, artemisinin alleviates type 2 DCM in rats by modulating the AGE-RAGE/HMGB1 axis, resulting in reduced oxidative stress, inflammation, and fibrosis.[44] Lindenenone attenuates cardiac hypertrophy and inflammation in diabetic mice by suppressing the MAPK/ATF6 pathway.[45] These distinct yet complementary mechanisms highlight the multitargeted therapeutic potential of sesquiterpenoids in counteracting the pathogenesis of DCM, establishing a solid experimental foundation for the development and clinical translation of natural product-based therapies.

Diterpenoids

Research on diterpenoids for DCM treatment remains relatively limited. Forskolin, a natural diterpenoid isolated from the roots of *Coleus forskohlii*, demonstrates strong antioxidant properties. It provides protection against streptozotocin-induced DCM in mice mainly by alleviating oxidative stress and suppressing myocardial fibrosis.[46]

Triterpenoids

Triterpenoids hold multitarget therapeutic potential against DCM. For example, astragaloside IV mitigates myocardial dysfunction in DCM rats by downregulating CD36-mediated ferroptosis.[47] In a type 2 diabetic rat model, it also enhances myocardial lipid metabolism, providing protection against DCM.[48] Asiaticoside exerts protective effects against DCM by activating the AMPK/Nrf2 pathway, which improves mitochondrial function, promotes autophagy, and reduces oxidative stress.[49] Similarly, platycodin D ameliorates type 2 diabetes-induced myocardial injury by activating the AMPK pathway, resulting in restored autophagic flux.[50] Celastrol alleviates DCM in mice mainly by inhibiting the ACE/Ang II/AGTR1 axis, thereby attenuating inflammatory responses, oxidative stress, and cardiomyocyte apoptosis.[51] Mogroside II mitigates cardiomyopathy in a type 2 diabetic model by suppressing cardiomyocyte apoptosis.[52] Ginsenosides hold significant cardioprotective potential against DCM. Specifically, ginsenoside Rg1 induces mesenchymal stem cells to secrete exosomal circNOTCH1, which promotes macrophage M2 polarization by activating the NOTCH signaling pathway, ultimately alleviating DCM.[53] Meanwhile, ginsenoside Rg3 activates PPAR-γ to enhance adiponectin signaling, protecting the heart from DCM-related injuries.[54] Nimbolide protects against DCM by modulating endoplasmic reticulum stress and mitochondrial function through the Akt/mTOR pathway.[55]

Terpenoids demonstrate distinct advantages in intervening in DCM due to the structural diversity of their isoprene units, which underlies their novel mechanisms and unique targeting profiles. Unlike flavonoids, terpenoids act on more advanced pathological processes, including gut microbiota regulation (e.g., paeoniflorin), non-coding RNA modulation (e.g., perillaldehyde affecting miRNAs), and emerging forms of programmed cell death (e.g., astragaloside IV suppressing ferroptosis). Moreover, various terpenoid subtypes broadly target key pathways ranging from metabolic inflammation (e.g., artemisinin acting on the AGE-RAGE axis) to cellular signaling (e.g., ginsenosides modulating exosome-mediated communication). Overall, with their abundant natural availability and structurally complex scaffolds, terpenoids offer a novel dimension of action and promising drug leads for the prevention and treatment of DCM, setting them apart from conventional polyphenolic compounds.

Phenylpropanoids

Phenylpropanoids, characterized by a C6–C3 skeleton as their fundamental structural unit, are widely distributed in medicinal plants, such as *Lonicera japonica*, *Salvia miltiorrhiza*, and *Cinnamomum cassia*. These compounds are classified into three major subclasses: phenylpropanoic acids, coumarins, and lignans. Owing to their widespread natural distribution, diverse biological activities, and favorable safety profile, phenylpropanoids have gained considerable attention for preventing and treating metabolic disease complications. Notably, they demonstrate promising cardioprotective properties within the pathological context of DCM.

Phenylpropanoic acids

Cinnamic acid hinders the progression of DCM through the synergistic interplay of four principal properties: cardioprotective, anti-inflammatory, antidyslipidemic, and antidiabetic actions.[56] Studies have demonstrated that chlorogenic acid may ameliorate DCM by modulating endoplasmic reticulum stress and associated pathways, including ER-phagy, and attenuating cardiomyocyte apoptosis in diabetic rat hearts.[57] Ferulic acid exerts anti-DCM effects via a dual mechanism. First, it modulates the PACS2/IP3R2/FUNDC1/VDAC1 pathway, ameliorating the hyperglycemia-induced structural and functional impairments of mitochondria-associated ER membranes and suppressing the activation of proapoptotic proteins, thereby alleviating cardiomyopathy in diabetic rats.[58] Second, it can correct spatially disorganized metabolic disturbances in myocardial tissues under DCM conditions, as revealed by integrated mass spectrometry.[59]

Coumarins

Umbelliferone, a coumarin compound predominantly isolated from *Angelica sinensis*, ameliorates DCM in rats by suppressing the JAK/STAT signaling pathway, thereby attenuating oxidative stress and inflammatory responses.[60]

Lignans

Schisandrin B, a dibenzocyclooctadiene lignan and a major bioactive constituent of *Schisandra chinensis* fruits, demonstrates significant anti-inflammatory, antioxidant, and cardioprotective properties. It alleviates DCM by specifically targeting MyD88, thereby suppressing MyD88-dependent inflammatory signaling.[61]

Phenylpropanoid derivatives

Salvianolic acid A enhances mitochondrial respiration and cardiac function in DCM by regulating CRYAB to inhibit the apoptotic pathway.[62] Salvianolic acid B provides protection against DCM through two distinct mechanisms. First, it attenuates myocardial fibrosis by promoting the deubiquitination of Smad7.[63] Second, it improves cardiac function by suppressing IGFBP expression and activity.[64] Echinacoside confers considerable protection against DCM in db/db mice, reducing cardiac apoptosis, oxidative stress,

and disordered lipid metabolism. Mechanistic studies have shown that it suppresses cardiomyocyte death by modulating the p53/p38 MAPK pathway and inhibits lipid accumulation through the PPAR-α/M-CPT-1 axis.[65] These results provide experimental evidence supporting further investigation of its mechanisms and support its potential for clinical translation.

This review synthesizes evidence that phenylpropanoids protect against DCM primarily by targeting inflammatory, apoptotic, and metabolic disturbances. Phenylpropanoic acids (e.g., cinnamic acid) and their derivatives (e.g., salvianolic acids) predominantly inhibit inflammatory signaling (e.g., MyD88, JAK/STAT) and regulate metabolic or apoptotic pathways to ameliorate ER stress, mitochondrial dysfunction, and fibrosis. Coumarins and lignans converge on suppressing oxidative stress and inflammation via similar pathways. Collectively, their cardioprotection is achieved through multimodal regulation of cardiomyocyte death, organelle homeostasis, and inflammatory cascades, underscoring their integrated therapeutic potential.

Alkaloids

Alkaloids, a prominent class of nitrogen-containing heterocyclic natural products, are widely distributed across plants, animals, and microorganisms. Owing to their potent pharmacological activities and well-elucidated mechanisms of action, they are extensively studied for the treatment of metabolic diseases and associated complications. These compounds show promising potential for multitarget intervention in the complex pathological processes of DCM. Rhyparochromine, an indole alkaloid, alleviates DCM by inhibiting ryanodine receptor 2 phosphorylation, thereby preserving cardiomyocyte calcium homeostasis as well as mitochondrial structure and function.[66] Rutaecarpine, a quinazoline alkaloid, enhances TRPV1-mediated autophagic flux, mitigating hyperglycemia-induced cardiomyocyte damage and oxidative stress.[67] The isoquinoline alkaloid berberine confers protection against DCM through three distinct mechanisms. First, it modulates SIRT3-dependent lipophagy to remodel myocardial lipid droplet homeostasis and alleviate cardiac lipotoxicity.[68] Second, it suppresses NLRP3 inflammasome-induced pyroptosis by regulating the mTOR/mitochondrial ROS axis.[69] Third, it inhibits inflammasome activation through the miR-18a-3p/GSDMD pathway, collectively attenuating DCM pathology.[70]

Polysaccharides

Polysaccharides, a class of macromolecular carbohydrates abundant in plants, fungi, and microorganisms, are well known for their diverse bioactivities, low toxicity, and favorable safety profile. These characteristics make them highly promising for the management of metabolic dysregulation and mitigation of associated organ damage. In DCM, polysaccharides confer protection by targeting core pathological features, particularly mitochondrial dysfunction, myocardial hypertrophy, and dysregulated signaling pathways. Lentinan alleviates DCM by mitigating CAV1/SDHA-mediated mitochondrial dysfunction, thereby restoring myocardial energy metabolism.[71] Astragalus polysaccharide counteracts myocardial hypertrophy in DCM models via targeted suppression of aberrant BMP10-mediated signaling.[72] Polygonatum polysaccharide enhances cyclic guanosine monophosphate–protein kinase G signaling in the myocardium of diabetic mice, improving cardiac structure and function as well as attenuating DCM pathology.[73]

Others

Curcumin, a polyphenolic compound derived from turmeric (*Curcuma longa*), ranks among the most extensively explored monomeric natural products. It exerts a wide range of cardioprotective effects, including improvement of glucose metabolism, reduction of oxidative stress and inflammation, inhibition of apoptosis and macrophage adhesion to endothelial cells, correction of dyslipidemia, and promotion of angiogenesis.[74,75] Mechanistically, curcumin alleviates myocardial dysfunction in diabetic rats by activating the Sirt1-Foxo1 and PI3K-Akt pathways, thereby mitigating oxidative stress and apoptosis.[76] Furthermore, it activates the Nrf2/HO-1 pathway to reduce ROS production, enhance antioxidant enzyme activity, and inhibit cardiomyocyte death.[77] Curcumin also modulates the pyroptosis pathway by regulating TRIM21 expression, thereby restraining inflammation-associated pathology.[78] Resveratrol, a natural polyphenol, demonstrates potent anti-inflammatory, antioxidant, anti-aging, and cardioprotective properties. A preclinical systematic review and meta-analysis revealed that its protective effects against DCM involve multiple signaling pathways, such as SIRT1/PGC-1α, SIRT3/TFAM, AMPK/mTOR, Nrf2, Akt, and MAPK, which collectively mediate antioxidative, anti-inflammatory, anti-apoptotic, and anti-fibrotic responses.[79–81] D-Pinitol confers protection against DCM through dual mechanisms: it upregulates cardiac optineurin to suppress endoplasmic reticulum stress and autophagy[82] and modulates the PI3K/Akt/mTOR pathway to attenuate apoptosis, fibrosis, oxidative stress, and cardiac dysfunction.[83] Gastrodin alleviates myocardial fibrosis by inhibiting the KLK8PAR1 axis in cardiac fibroblasts, thereby inhibiting their differentiation, collagen production, and migration.[84] Concurrently, it enhances the antioxidant capacity of cardiomyocytes via GSK-3β-mediated Nrf2 nuclear translocation, counteracting hyperglycemia-induced injury.[85]

Rhein also ameliorates mitochondrial dynamics while counteracting apoptosis and hypertrophy.[86] Tanshinone IIA attenuates DCM via SIRT1-dependent ER stress suppression.[87] Z-Ligustilide alleviates high glucose/lipid-induced myocardial dysfunction by inhibiting oxidative damage, inflammatory responses, and fibrotic processes.[88] Epigallocatechin gallate attenuates fibrosis via blockade of the TGF-β1/JNK pathway.[89] Apocynin suppresses the ASK1–p38/JNK signaling axis to mitigate oxidative stress, apoptosis, hypertrophy, and fibrosis.[90] Punicalagin and paeonol enhance Opa1-mediated mitochondrial fusion—acting through the PTP1B–Stat3 and CK2α–Stat3 pathways, respectively—to ameliorate DCM pathology.[91,92] 6-Gingerol has been shown to attenuate ferroptosis and inflammation in cardiomyocytes, potentially through activation of the Nrf2/HO-1 pathway.[93] Polydatin, a resveratrol glucoside, exerts its protective effect in a Caveolin-1-dependent manner.[94] By targeting diverse molecular pathways, these compounds exemplify a multifaceted and multitarget therapeutic strategy for DCM.

Future directions

Despite notable advancements, several key issues remain unresolved. First, current mechanistic understanding is largely limited to the effects of single compounds on isolated signaling pathways. Given the multifactorial pathology of DCM, the synergistic or antagonistic interactions within multipathway networks remain poorly elucidated. Second, for important compounds such as salvianolic acid B and berberine, the primary molecular targets and upstream regulators remain poorly characterized, which hampers rational drug design. A substantial translational gap also persists, as current evidence predominantly derives from animal and cellular studies, highlighting the urgent need for clinical validation. Moreover, the

potential for combination therapy with standard medications, such as SGLT2 inhibitors and metformin, and the mechanistic basis of such interactions represent a promising but largely unexplored research direction. Future studies should employ more systematic and precise methodologies, with greater emphasis on clinical translation. Prioritizing preclinical validation in large animal models, followed by well-designed clinical trials, will be crucial for providing compelling evidence supporting the clinical use of these natural products. Through interdisciplinary collaboration and coordinated efforts between academia and industry, natural products show great potential for developing innovative approaches for the early intervention and integrated management of DCM.

Limitations

This review summarizes research advances from the past five years. However, several inherent limitations need to be acknowledged. First, the included studies predominantly rely on *in vitro* and rodent models, which may not fully recapitulate the complexity and chronicity of human DCM pathophysiology, potentially limiting the translational relevance of the findings. Second, available evidence largely stems from investigations of isolated compounds acting on single or limited signaling pathways. This approach may fail to capture potential synergistic or antagonistic interactions within the intricate multipathway network underlying DCM pathogenesis. Third, for many promising compounds, detailed pharmacokinetic profiles, optimal dosing regimens, and long-term safety data in disease-relevant contexts remain poorly explored. In addition, comparative efficacy analyses among different natural products or between natural products and standard clinical therapies are notably limited. Addressing these gaps is crucial for advancing these natural products from the bench to the bedside.

Conclusions

This review provides a systematic overview of natural products reported over the past five years that have shown efficacy against DCM. Structurally, these compounds are classified into flavonoids, terpenoids, phenylpropanoids, alkaloids, and polysaccharides. Flavonoids are the most extensively investigated category, encompassing the following subclasses: flavonols (e.g., quercetin, icariin), flavones (e.g., baicalein, baicalin), and isoflavones (e.g., puerarin). Terpenoids are the second-largest group, including triterpenes (e.g., astragaloside IV, ginsenoside Rg3) and sesquiterpenes (e.g., artemisinin, β-caryophyllene). Owing to their diverse origins and chemical structures, these compounds interact with the complex pathological network of DCM via multitarget and multilevel mechanisms, providing a rich molecular resource for drug discovery. In terms of mechanisms, these compounds exert protective effects not only through common pathways—such as ameliorating insulin resistance, correcting glycolipid metabolic disorders, and mitigating oxidative stress and inflammation—but also through precise interventions in specific pathological processes. These include the regulation of cardiomyocyte death (e.g., apoptosis, pyroptosis, and ferroptosis), enhancement of mitochondrial function, modulation of autophagy, and suppression of myocardial fibrosis and calcium dysregulation. Research spanning molecular, cellular, and animal models has systematically demonstrated the potential of natural products to slow or even reverse the progression of DCM. These insights deepen our understanding of DCM pathology and provide a solid theoretical foundation for developing natural product-based therapeutics.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization (CH, RZ), writing-original draft preparation (RZ, HL, YZhao, LM, YZheng), writing-review and editing (CH), and supervision and funding acquisition (CH). All authors have read and agreed to the published version of the manuscript.

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