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REVIEW

Mechanistic Insights into Flavonoid Subclasses as Cardioprotective Agents Against Doxorubicin-Induced Cardiotoxicity: A Comprehensive Review

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Abstract: Doxorubicin (DOX) is an anthracycline chemotherapeutic agent widely used for treating various malignancies due to its remarkable efficacy. However, the dose-limiting cardiotoxicity induced by DOX remains a critical clinical concern with limited therapeutic strategy. Several molecular mechanisms underlying the pathogenesis of doxorubicin-induced cardiotoxicity (DIC) have been proposed, including oxidative stress, dysregulation of Top2β, mitochondrial damage, imbalance of calcium homeostasis, ferroptosis, and inflammatory responses. Increasing studies have posed the promise of the natural products flavonoids against DIC attributed to its advantages in antioxidant activity as well as anti-cancer properties. This paper reviews relevant publications to date and comprehensively summarizes the evidence from preclinical and clinical studies in support of the cardioprotective effect of seven flavonoids subclasses against DIC, including flavones with 18 compounds, flavonols with 11 compounds, isoflavones with 7 compounds, flavanones with 6 compounds, chalcones with 3 compounds, flavanols with 2 compounds and anthocyanins with 2 compounds. Specially, several lines of evidence have also demonstrated the anti-cancer property of flavonoids in addition to the cardioprotective property. This review synthesizes comprehensive mechanistic and translational insights to inform future preclinical and clinical investigations aiming at integrating flavonoid-based interventions into oncotherapeutic regimens. The accumulated evidence underscores flavonoids as promising candidates for DIC as well as adjuvant cancer therapy.

Keywords: doxorubicin, cardiotoxicity, flavonoids, mechanism, cardioprotection

Introduction

Doxorubicin (DOX), a member of the anthracycline family, is one of the most effective chemotherapeutic agents for treating various malignancies, including hematological cancers and solid tumors.[1] Despite its therapeutic efficacy, DOX is associated with a dose-dependent cardiotoxicity, which remains a significant clinical challenge.[2] Pharmacologically, intravenous DOX is quickly metabolized into the doxorubicinol (DOXol) by utilizing an enzyme NADPH-dependent aldo reductases.[3] Although DOX the plasma concentration of DOX falls quickly after administration, DOXol exhibits higher hydrophilicity than DOX, resulting in slower clearance from cardiomyocytes and sustaining higher concentrations within myocardial tissue particularly after repeated injection.[4] Both DOX and DOXol have the ability to inhibit DNA biosynthesis, form free radicals and disrupt the function of the ion pump in the sarcoplasmic reticulum of cardiac cells, inducing cell death.[5] Consequently, the clinical concern with cardiotoxicity limits the cumulative dose of DOX to 400–700 mg/m² to minimize risks of acute and chronic cardiac damage.[6] Acute toxicity manifests within days of

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administration as arrhythmias, myocarditis, or pericarditis, whereas chronic toxicity, occurring months or years later, may lead to irreversible heart failure.[7] The underlying mechanisms of DOX-induced cardiotoxicity (DIC) are multifaceted, involving oxidative stress, mitochondrial dysfunction, calcium homeostasis dysregulation, intracellular iron overload, and DNA damage mediated through topoisomerase IIβ (Top2β). Of these, oxidative stress is a central driver, initiated by DOX's quinone structure undergoing redox cycling, producing excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS).[8] These radicals damage cellular components, including lipids, proteins, and DNA, resulting in cardiomyocyte apoptosis and necrosis. Given these limitations, extensive research has focused on developing cardioprotective strategies to mitigate DIC without compromising its anti-tumor efficacy. Conventional approaches include the use of liposomal DOX, the restriction of cumulative doses, and the co-administration of the iron chelator dexrazoxane, an FDA-approved cardioprotective agent.[6,9] However, these strategies have limitations, such as potential interference with DOX's anti-tumor activity and insufficient protection against cardiac injury.[10,11] Consequently, there is a growing interest in exploring compounds with anti-tumor and cytoprotective properties.

Flavonoids, a class of polyphenolic compounds widely distributed in fruits, vegetables, and medicinal plants, have emerged as promising candidates for cardioprotection.[12,13] Chemically, flavonoids consist of a fifteen-carbon skeleton arranged as two benzene rings connected by a heterocyclic pyran ring.[14] Based on structural differences, flavonoids are categorized into subgroups such as flavones, flavonols, flavanones, and anthocyanins.[15] Several studies have demonstrated the pharmacological benefits of flavonoids, including antioxidant, anti-inflammatory, anti-apoptotic, anti-cancer, and iron-chelating activities, which make them particularly suitable for combating DIC.[1] Mechanistically, flavonoids exert their cardioprotective effects by scavenging ROS, chelating free iron to prevent Fenton reactions, modulating apoptotic pathways, and attenuating mitochondrial dysfunction.[11] For instance, quercetin, luteolin, and rutin have been shown to enhance the expression of Nrf2 and associated antioxidant enzymes, such as superoxide dismutase (SOD) and heme oxygenase 1 (Hmox1), while inhibiting pro-apoptotic proteins like Bax and Caspases.[16,17] Additionally, flavonoids stabilize calcium homeostasis to mitigate calcium overload, which is pivotal in preventing cardiac contractile dysfunction.[18,19]

Despite the promising results from in vitro and in vivo studies, the clinical translation of flavonoids as cardioprotective agents against DOX toxicity remains in its infancy. Challenges such as bioavailability, pharmacokinetics, and potential interactions with chemotherapy necessitate further research. Previous reviews summarized relevant studies with limited data from particular perspective.[1,11,16] This review aims to comprehensively evaluate the role of flavonoids in mitigating DIC, focusing on their mechanisms of action, preclinical evidence, and potential for clinical application. By integrating insights from molecular studies and translational research, we aim to highlight flavonoids as valuable candidates for enhancing the safety and efficacy of DOX-based chemotherapy regimens.

Overview of Mechanisms Underlying DIC

As shown in Figure 1, the cardiotoxicity mechanism of DOX is a complex and multifaceted process involving the interplay of various factors, including oxidative stress, dysregulation of Top2β, mitochondrial damage, imbalance of calcium homeostasis, ferroptosis, and inflammatory responses.[6] Understanding these mechanisms is crucial for developing effective preventive and therapeutic strategies to mitigate DIC.

ROS Generated by Oxidative Stress

Oxidative stress plays a central role in DIC, encompassing several key aspects.[6,8] First, DOX accumulates in mitochondrial compartments of cardiomyocytes, leading to excessive production of ROS, particularly through the redox cycling of complex I in the electron transport chain, which disrupts ATP synthesis.[20] Second, DOX generates semiquinone radicals via its quinone moiety, which react with oxygen to produce superoxide anions (O_2^-), further converting into hydrogen peroxide (H_2O_2) and other ROS.[21] Third, DOX induces the upregulation of nitric oxide synthase (Nos), increasing nitric oxide (NO) levels, which react with superoxide anions to form peroxynitrite ($ONOO^-$), exacerbating oxidative damage.[8] Simultaneously, NADPH oxidases (Noxs) are activated, catalyzing the oxidation of DOX's quinone structure, and serve as a major source of ROS.[8,22] Furthermore, DOX significantly depletes endogenous antioxidants such as glutathione (GSH) and catalase (CAT), leading to an imbalance between oxidative and antioxidative systems.[23,24] The Nrf2

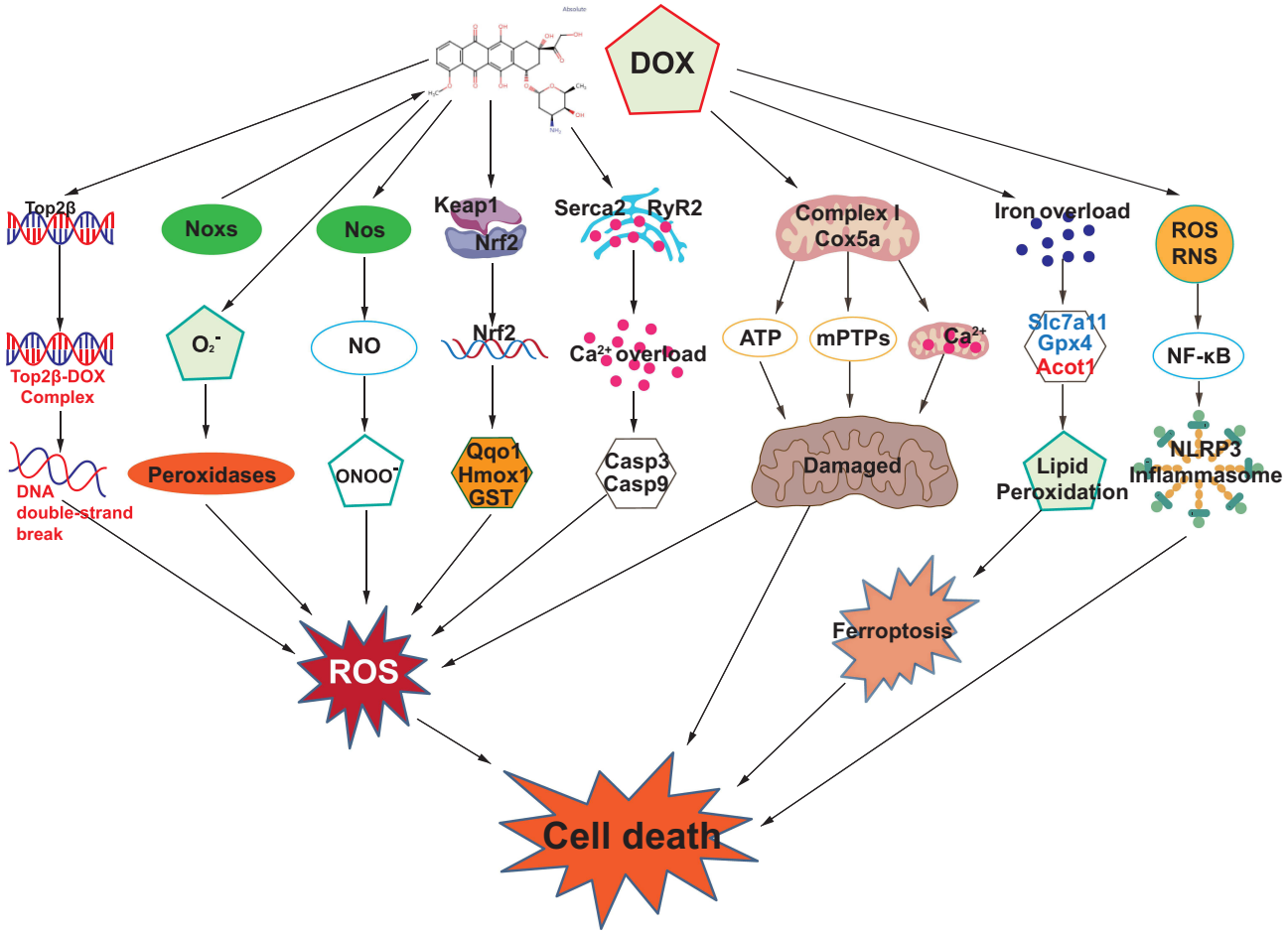

Figure 1 Core mechanisms involved in doxorubicin-induced cardiotoxicity.

transcription factor plays a pivotal role in stabilization of DOX-induced oxidative stress by dissociating from kelch-like ECH-associated protein 1 (Keap1) and translocating into the nucleus to activate antioxidant genes, including NAD(P)H dehydrogenase, quinone 1 (Nqo1), Hmox1, and glutathione S-transferase (GST).[25] Additionally, DOX induces mitochondrial and ER damage, disrupting calcium homeostasis, and interacts with iron metabolism-related proteins, resulting in iron overload, which further amplifies ROS generation.[8,26,27] These interconnected mechanisms collectively lead to oxidative injury, dysfunction, and apoptosis in cardiomyocytes, ultimately contributing to DIC.

Top2β

DNA topoisomerase particularly Top2β has garnered significant attention for its involvement in cardiac damage in DIC. DOX interacts with Top2β to form a stable DNA-Top2β-DOX ternary complex, inhibiting the DNA helicase activity of Top2β, which results in DNA double-strand breaks and subsequent cell death.[28] In cardiac tissue, the relatively high expression levels of Top2β render cardiomyocytes especially susceptible to DIC.[29] Moreover, DOX-mediated Top2β inhibition may activate stress responses, induce transcriptional alterations, and disrupt signaling pathways involving P53, IGFBP, PDE10A, cAMP/PKA/FoxO3, cGMP/PKG/FoxO3, and PPARγ.[4,30–32] These disruptions lead to mitochondrial dysfunction and oxidative stress.[20] Notably, studies have demonstrated that cardiomyocyte-specific deletion of the Top2β gene protects mice from DOX-induced progressive heart failure, underscoring the mediating role of Top2β in DIC.[33]

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Mitochondrial Damage

Previous studies have documented that mitochondrial damage is closely associated with DIC, involving several molecular mechanisms.[3] First, DOX binds to mitochondrial DNA, inhibiting the activity of respiratory chain complexes I to IV and downregulating the expression of cytochrome c oxidase subunit 5A (Cox5a). These effects lead to mitochondrial dysfunction, increased production of ROS, and subsequent oxidative stress, ultimately resulting in myocardial injury.[34,35] Second, DOX's metabolite, doxorubicinol, accumulates in the heart, disrupting mitochondrial structure, impairing mitochondrial dynamics and autophagy, and preventing the effective clearance of damaged mitochondria, thereby exacerbating mitochondrial injury.[4] Additionally, DOX interferes with mitochondrial calcium homeostasis, causing calcium overload, which triggers the opening of mitochondrial permeability transition pores (mPTPs). This results in mitochondrial membrane depolarization, matrix swelling, outer membrane rupture, and the activation of apoptotic signaling molecules such as cytochrome c (Cyt C) and Caspase-3, ultimately inducing cardiomyocyte apoptosis.[36,37] Finally, DOX activates pro-apoptotic pathways, including P53 signaling, while suppressing the expression of key regulators of mitochondrial biogenesis and energy production, such as PGC1α and PGC1β. These disruptions affecting mitochondrial energy output further exacerbate cardiac injury.[38,39]

Calcium Signaling Dysregulation

The molecular mechanisms underlying calcium signaling dysregulation in DIC involve multiple levels of disruption. First, DOX disrupts intracellular calcium dynamics by inhibiting the expression of SERCA2 in cardiomyocytes, thereby impairing sarcoplasmic reticulum (SR)-mediated calcium regulation.[40] Second, DOX directly interacts with cardiac RyR2 and SERCA2, altering SR calcium handling through thiol oxidation of these proteins.[41,42] Furthermore, DOX activates PARP signal, exacerbating calcium-handling disruptions.[43] DOX also influences calcium influx, inhibits SR calcium release, and suppresses Na^+/Ca^{2+} exchange, which collectively affect the duration of action potential and impair diastolic function in cardiomyocytes.[44,45] In diastolic dysfunction, DOX-treated cardiomyocytes exhibit impaired buffering of intracellular free Ca^{2+} ions, underscoring the importance of monitoring diastolic performance for early detection of DIC.[46] Additionally, DOX damages intracellular calcium mobilization and buffering during the contraction-relaxation cycle under β-adrenergic receptor stimulation, as well as calcium transient responses.[47–49] These calcium signaling abnormalities amplify ROS production, activate apoptotic pathways involving Caspase-3 (CASP3) and Caspase-9 (CASP9), and ultimately result in cardiomyocyte dysfunction.[50–53]

Ferroptosis

The molecular mechanisms of ferroptosis in DIC involve the interplay of multiple metabolic processes, primarily iron metabolism, GSH metabolism, and lipid metabolism.[54] In terms of iron metabolism, DOX promotes iron accumulation in cardiomyocytes by inhibiting iron export proteins, such as ferroportin (FPN), and increasing iron uptake, leading to iron overload. This iron overload generates hydroxyl radicals through the Fenton reaction, triggering lipid peroxidation.[55–57] Regarding GSH metabolism, DOX inhibits cysteine uptake and the activity of solute carrier family 7 member 11 (Slc7a11), which disrupts GSH synthesis and transport, thereby inducing ferroptosis.[58] DOX also suppresses the activity of glutathione peroxidase 4 (Gpx4), a key enzyme that inhibits ferroptosis by detoxifying lipid peroxides.[59] Impairment of Gpx4 activity results in the accumulation of lipid peroxidation products, further promoting ferroptosis.[54] In lipid metabolism, DOX upregulates Acsl4 while downregulating Acot1, leading to an increase in polyunsaturated fatty acids (PUFAs), which serve as substrates for lipid peroxidation, thereby exacerbating ferroptosis.[54,60] Additionally, DOX may regulate ferroptosis by affecting the iron-regulatory protein (IRP)-iron-responsive element (IRE) system, Nrf2 signaling pathway, and mitochondrial function.[61,62] These interconnected molecular mechanisms collectively drive ferroptosis in cardiomyocytes, contributing to DIC.

Inflammation

Inflammatory responses are significantly involved in DIC. DOX treatment increases the production of ROS and RNS, which activate NF-κB signaling pathway and induce the release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6).[21] These cytokines directly contribute to

programmed cell death processes in cardiomyocytes, including apoptosis, autophagy, and necrosis.[63,64] The inflammatory responses also impair crosstalk between endothelial cells and cardiomyocytes, disrupting vascular endothelial function and promoting atherosclerosis and coronary artery damage.[65] Furthermore, DOX-induced oxidative stress activates the Nlrp3 inflammasome, leading to pyroptosis, an inflammatory form of cell death, accompanied by the release of IL-1β and interleukin 18 (IL-18).[21,66] This exacerbates inflammation and amplifies cardiac injury, further contributing to DIC.

Potentials of Flavonoids in the Treatment of DIC

Flavonoids are a class of polyphenolic plant secondary metabolites widely found in fruits, vegetables, tea, red wine, and various herbs.[14,15] Chemically, flavonoids are based on a fifteen-carbon skeleton consisting of two benzene rings (A and B, as illustrated in Figure 2) connected via a heterocyclic pyran ring (C).[12] Based on their chemical structures, flavonoids can be classified into several subgroups (Figure 3), including flavones, flavonols, flavanones, isoflavones, flavanols, chalcones, and anthocyanins.[15] Pharmacologically, flavonoids are renowned for their diverse health-promoting and disease-preventing potential, including antioxidant, anti-inflammatory, anti-tumor, cardiovascular, neuroprotective, antibacterial, and antiviral effects.[67] In recent years, flavonoids have attracted increasing attention for their role in mitigating DIC. The primary findings are summarized as Table 1.

Isoflavones

Daidzein

Daidzein, 7-hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one is a naturally occurring isoflavone found prominently in soybeans and legumes, exhibits significant therapeutic potential due to its structural similarity to estrogen.[161] Acting as a phytoestrogen, daidzein modulates estrogen receptor activity and displays a diverse range of pharmacological effects, including anti-tumor, antioxidant, anti-inflammatory, and cardioprotective properties.[162] As documented, daidzein supports cardiovascular health by improving lipid metabolism, reducing oxidative stress, and enhancing endothelial function.[163] Previous studies have demonstrated cardioprotective effects of Daidzein against DIC through various molecular mechanisms. Two key studies highlight its potential in mitigating cardiac dysfunction, oxidative stress, apoptosis, and autophagy, using both in vivo and in vitro models. In one study involving C57BL/6J mice and H9c2 cardiomyoblast cells, daidzein significantly improved cardiac function by preserving left ventricular ejection fraction (LVEF) and reducing inflammation, fibrosis, and oxidative damage caused by DOX. Mechanistically, daidzein enhanced mitochondrial function and energy metabolism by upregulating Sirt3 and its downstream target FoxO3.[68] This pathway played a crucial role in alleviating oxidative stress and restoring metabolic homeostasis, including glucose, lipid, and ketone body metabolism. These findings suggested that daidzein exerted its cardioprotective effects through metabolic regulation and antioxidant activity. Another study using Sprague-Dawley rats and H9c2 cells further explored daidzein's

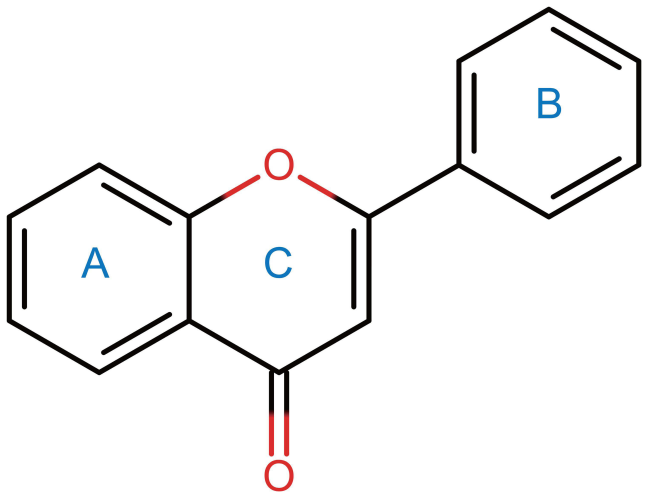

Figure 2 Common chemical structure of flavonoids.

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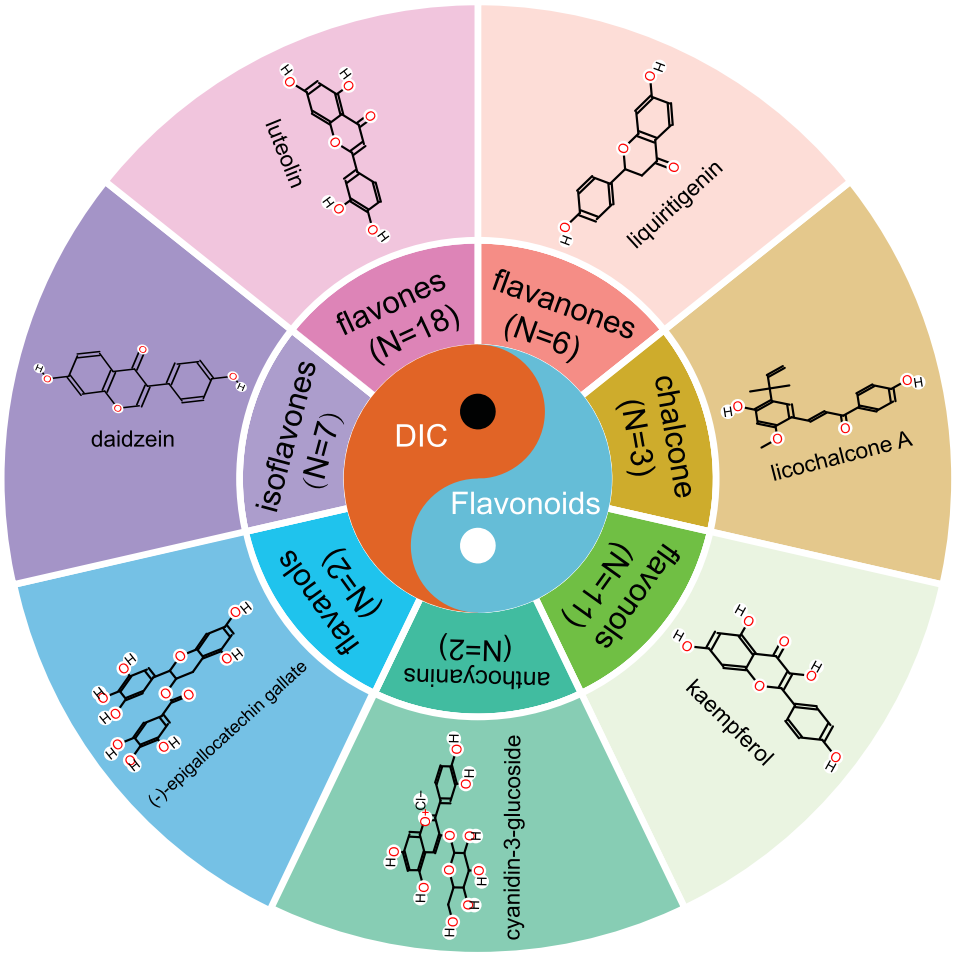

Figure 3 Diagram summarization of flavonoids for the treatment of doxorubicin-induced cardiotoxicity.

anti-apoptotic and anti-autophagic mechanisms. Rats treated with low-dose daidzein showed improved cardiac function and reduced myocardial damage. In vitro, daidzein reduced DOX-induced autophagy and apoptosis, as evidenced by lower levels of Bax, LC3 II, and cleaved Caspase-3, alongside increased Bcl-2 and cyclin D1 expression. These effects were mediated by the inhibition of the PI3K/Akt pathway, as activation of this pathway with an Akt agonist reversed the cardioprotective effects of daidzein.[69]

Calycosin

Calycosin is a typical phytoestrogen and the major bioactive isoflavonoids in the dry root extract of *astragalus membranaceus* which is widely used for the treatment of hypertension, nephritis, cancer, diabetes, cirrhosis, and many other disorders in traditional Chinese medicine (TCM).[164] Calycosin and its derivatives have multiple biological effects, such as antioxidant, pro-angiogenesis, anti-tumour, antidiabetic, hepatoprotective, neuroprotective, and anti-inflammatory effects.[165] For cancer, research has demonstrated its potential in modulating various signaling pathways, such as the inhibition of cell proliferation and the induction of apoptosis in cancer cells.[166] Furthermore, calycosin has shown promising cardioprotective effects, including the prevention of myocardial injury and the improvement of heart function under conditions like ischemia/reperfusion injury and heart failure.[167] Additionally, its role in regulating oxidative stress and inflammatory responses positions it as a valuable therapeutic agent for conditions associated with chronic inflammation and oxidative damage.[166] Calycosin has been studied for its cardioprotective effects against DIC through multiple mechanisms. Two key studies highlighted its potential in mitigating oxidative stress, apoptosis, and autophagy dysregulation, employing both in vivo and in vitro models. In one study, calycosin significantly improved the viability of H9c2

Table 1 Cardioprotective Effects of Flavonoids Against Doxorubicin-Induced Cardiotoxicity

Flavonoids	Compounds	StudyDesign	Marker	Signal	Mechanism	Ref.
	Daidzein	In vivo(mice)	↓CK, ↓LDH, ↓HBDH, ↓AST, ↓ALP, ↓ROS	↑SIRT3/FOXO3a	Mitochondrial dysfunction, Inflammation, Oxidative stress, Apoptosis, Fibrosis	[68]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓CK, ↓LDH, ↓HBDH, ↓AST, ↓ALP			
		In vivo(rat)	↑LVSP, ↑+dp/dt, ↓LVEDP, ↓-dp/dt, ↓LC3II	↓PI3K/AKT	Oxidative stress, Autophagy, Apoptosis	[69]
		In vitro(H9c2)	↑Cell viability, ↓cleaved Caspase3, ↓Bax, ↑Bcl-2, ↓fibrosis, ↑cyclin D1			
	Calycosin	In vivo(mice)	↓AST, ↓LDH, ↓MDA, ↑GSH-PX, ↑CAT, ↑SOD	↑SIRT1	Oxidative stress, Inflammation	[70]
		In vitro(H9c2)	↑Cell viability, ↓Bax, ↑Bcl-2, ↑GSH-Px, ↑CAT, ↑SOD, ↓AST, ↓LDH, ↓MDA, ↓ROS, ↓NLRP3			
		In vivo(zebrafish)	↑survival, ↑FS, ↑EF, ↑HR, ↓Nppa, ↓Nppb	/	Autophagy	[71]
		In vitro(H9c2)	↑Cell viability, ↑autophagy, ↑LC3-II, ↑Atg7			
	Ononin	In vivo(rat)	↑LVEF, ↑LVFS, ↓ER stress, ↓LDH	↑SIRT3	Oxidative stress	[72]
		In vitro(H9c2)	↑Cell viability, ↓ER stress, ↓apoptosis, ↓Bax, ↑Bcl-2, ↓GRP78, ↓CHOP			
	8-Formylophiopogonanone B	In vivo(mice)	↓AST↓, ALT, ↓MDA/GSH/SOD, ↓Caspase-3	/	Oxidative stress, Apoptosis	[73]
		In vivo(mice)	↑LVEF, ↑FS↓CK-MB, ↓LDH, ↓HBDH, ↓fibrosis, ↓IL-1β, ↓IL-6, ↓HMOX1	/	Inflammation, Fibrosis	[74]
	Genistein	In vivo(rat)	↑LVSP, ↑+dp/dt, ↓LVEDP, ↓dp/dt, ↓Caspase3, ↓Bax, ↑Bcl-2, ↓LC3II	↓ERK1/2, ↑STAT3	Autophagy, Apoptosis	[75]
		In vitro(H9c2)	↑Cell viability, ↓autophagy, ↓apoptosis, ↑c-Myc			
		In vivo(mice)	↓ROS, ↓LPO, ↓4-hydroxynonenal-protein adducts, ↓TNF-α, ↓IL-6, ↓IL-8, ↑NQO1, ↑Bcl-2, ↓Bax, ↓cleaved Caspase-3	↑Nrf-2/HO-1, ↓ERK1/2, ↑AKT	Apoptosis, Inflammation	[76]
	Puerarin	In vivo(mice)	↓CK-MB, ↑ATP, ↑GSH, ↓GSSG, ↓Caspase-3	↑PKCε, ↑p-PKCε	Autophagy, Mitochondrial dysfunction, Oxidative stress	[77]
		In vitro(H9c2)	↑Cell viability, ↓LDH, ↓ROS, ↓Caspase-3, ↑LC3II, ↓P62, ↑14-3-3γ			
	Irigenin	In vivo(mice)	↓cTnI, ↓LDH, ↓CK-MB, ↓CPK, ↓BNP, ↓ANP, ↓MDA↓, MHC-β, ↓Caspase-3, ↓Bax, ↓PARP, ↓IL-18, ↓TNF-α, ↑Bcl-2, ↑SOD, ↑GSH, ↑GSH-GPx, ↑EF, ↑FS	↑miR-425, ↓RIPK1	Oxidative stress, Apoptosis, Inflammation, Fibrosis	[78]
		In vitro(HL-1)	↓ROS, ↓IL-1β, ↓IL-6, ↓TNF-α			

(*Continued*)

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Table 1 (Continued).

Flavonoids	Compounds	StudyDesign	Marker	Signal	Mechanism	Ref.
Flavone	Baicalin	In vivo(rat)	↓LDL-C, ↓TG, ↓IL-1β, ↓IL-6, ↓TNF-α, ↓MDA, ↑SOD	↑PI3K/AKT/Nrf2, ↓NF-κB, ↓MAPK	Oxidative stress, Apoptosis, Inflammation	[79]
		In vivo(mice)	↑EF, ↑FS, ↓fibrosis, ↑SLC7A11, ↑GPX4	↓AT1R	Ferroptosis, Oxidative stress	[80]
		In vitro(H9c2)	↓ROS, ↓Fe2+, ↓MDA, ↑GSH, ↓Caspase-3			
		In vivo(mice)	↓cTn-I, ↓CK-MB, ↓LDH, ↓AST, ↓TLR4, ↓IL-1β, ↓DKK1, ↓MDA, ↑β-catenin, ↑GSH	↓TLR4/NF-κB, ↑Wnt/β-catenin	Oxidative stress, Inflammation	[81]
	Baicalein	In vitro (Chick cardiomyocytes)	↑Cell viability, ↓ROS, ↓LDH, ↓apoptosis	↓JNK	Mitochondrial dysfunction, Oxidative stress	[82]
		In vivo(mice)	↓CK-MB, ↓LDH, ↓AST, ↓ALT, ↑HO-1, ↓p53, ↓Caspase-3, ↓PARP, ↓Bax, ↑Bcl-2	↑Nrf2, ↓NF-κB	Oxidative stress, Apoptosis, Inflammation	[83]
	Isoorientin	In vivo(mice)	↑HR, ↓QT, ↓fibrosis, ↓AST, ↓CK, ↓CK-MB, ↓LDH, ↓cTnT	↓p38 MAPK/JNK, ↑Nrf2, ↓AKT, ↓STAT3	Oxidative stress, Apoptosis	[84]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↑MMP, ↑TGF-β3, ↑Bcl-xL, ↓cleaved Caspase-3			
	Vaccarin	In vivo(mice)	↑LVEF, ↑LVFS, ↑LVPWd, ↑LVPWs, ↓LVEDs, ↓LVEdd, ↓BNP, ↓MDA, ↑SOD	↓p38 MAPK	Oxidative stress, Apoptosis, Mitochondrial dysfunction	[85]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓Bax, ↑Bcl-2, ↓Caspase-3, ↓MMP			
	Chrysin	In vivo(rat)	↓MDA, ↓CKMB, ↓LDH, ↑GSH, ↑SOD, CAT, ↑GPx, ↑GR, ↓p53, Puma, ↓Noxa, ↓Cytochrome C, ↓Caspase-3, ↑Bcl-2, ↓Bax↓	↓p38 MAPK/JNK, ↓NF-κB, ↓VEGF/PTEN, ↑AKT	Oxidative stress, Apoptosis	[86]
	Jaceosidin	In vivo(mice)	↑EF, ↑+dP/dt, ↓LVEDP, ↑SOD, ↑GSH, ↑Gpx1, ↑Nrf2, ↓MDA, ↓CK, ↓LDH, ↑HO-1, ↑Bcl-2, ↓Bax↓, ↓Caspase-3,	↑SIRT1, ↓NF-κB p65	Oxidative stress, Inflammation, Apoptosis	[87]
		In vitro(Nrcm)	↓ROS, ↓TNF-α, ↓IL-6			
	Chrysoeriol	In vitro(H9c2)	↑Cell viability, ↓ROS↓MDA, ↑SOD, ↑Gpx, ↓LDH, ↓MDA	/	Oxidative stress, Apoptosis	[88]
	Pinocembrin	In vivo(mice)	↑LVEF, ↑LVFS, ↓LVIDd, ↓LVIDs, ↓LDH, ↓CK-MB, ↓IL-1β, ↓IL-18, ↓fibrosis, ↓LDH, ↓CK-MB	↑Nrf2/SIRT3	Oxidative stress, Inflammation	[89]
		In vitro(H9c2)	↓ASC, ↓cleaved Caspase-1, ↓GSDMD-N, ↓NLRP3			
	7, 8-Dihydroxyflavone	In vitro(H9c2)	↑Cell viability, ↑MMP, ↑OPA1	↑AKT, ↑STAT3, ↓p38 AMPK, ↓ERK	Mitochondrial dysfunction	[90]
	OroxylinA	In vivo(mice)	↑EF, ↑+dP/dt, ↑-dP/dt, ↑LVSP, ↓LDH, ↓CK-MB, ↓4-HNE, ↓nitrotyrosine, ↑GSH, ↑Gpx, ↑SOD	↑cAMP/PKA/SIRT1, ↑Nrf2	Oxidative stress, Inflammation, Apoptosis	[91]
		In vitro(H9c2)	↓ROS, ↑HO-1, ↑NQO1, ↓TNF-α, ↓IL-6, ↓IL-1β, ↑Bcl-2			
	Acacetin	In vivo(mice)	↑LVEF, ↑%FS, ↓fibrosis	↑SIRT1/AMPK/Nrf2	Oxidative stress, Apoptosis	[92]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↑HO-1, ↑SOD1, ↑SOD2, ↑Bcl-2, ↓Bax, ↓cleaved Caspase-3			

	Dihydromyricetin	In vivo(mice)	↑LVEF, ↑LVFS, ↓LVIDd, ↓LVIDs	↑AMPK, ↓mTOR	Oxidative stress, Apoptosis, Autophagy	[93]
		In vitro(AC16)	↑Cell viability, ↓ROS, ↓apoptosis, ↑Bcl-2, ↓Bax, ↓cleaved Caspase-3, ↑Beclin-1, ↑LC3-II			
		In vivo(rat)	↑LVEF, ↑LVFS, ↓%fibrosis	↑SIRT1	Inflammation, Apoptosis	[94]
		In vitro(H9c2)	↑Cell viability, ↓Bax/Bcl-2, ↓NLRP3, ↓Caspase-1, ↓IL-1β, ↓IL-18			
		In vivo(mice)	↓ALT, ↓LDH, ↓CK-MB	↓MDM2, ↑ARC	Apoptosis, Oxidative stress	[95]
		In vitro(H9c2)	↑Cell viability			
	Apigenin	In vivo(mice)	↓TnT, ↓BNP, ↓CK-MB, ↑LVEF, ↑FS	↑SIRT1/Atf5/UPRmt	Oxidative stress, Mitochondrial dysfunction	[96]
		In vivo(mice)	↓fibrosis, ↓Caspase-1, ↓NLRP3, ↓GSDMD	↓GSK-3β/NF-κB	Inflammation, Pyroptosis	[97]
		In vitro(H9c2)	↓TNF-α, ↓IL-6, ↓IL-1β, ↓IL-18, ↓Caspase-1, ↓NLRP3, ↓GSDMD			
		In vivo(rat)	↑EF, ↑FS, ↑LVEF, ↑LVFS, ↑GSH, ↑SOD, ↓LDH, ↓CK-MB, ↓cTn-I, ↓ALT, ↓AST, ↓MDA, ↑SOD, ↓Bax, ↑Bcl-2, ↓Caspase-3, ↓fibrosis	↑PI3K/AKT/mTOR	Oxidative stress, Inflammation, Fibrosis	[98]
	Scutellarin	In vivo(rat)	↓LDH, ↓MDA, ↓cTnT, ↑LVEF, ↑LVFS	/	Oxidative stress	[99]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓MDA, ↑SOD, ↑MMP, ↓γ-H2AX, ↓Bax/Bcl-2, ↓Caspase-3, ↓Beclin1, ↓LC3-II/LC3-I, ↑p62	↑AKT, ↑mTOR	Oxidative stress, Mitochondrial dysfunction, Apoptosis, Autophagy	[100]
		In vitro(CFs)	↑Cellviability, ↓ROS, ↓MDA, ↑SOD, ↑MMP, ↓γ-H2AX, ↓Bax/Bcl-2, ↓Caspase-3, ↓Beclin1, ↓LC3-II/LC3-I, ↑p62			
	Icariin	In vitro(H9c2)	↑Cell viability, ↓ROS, ↓mPTP, ↓Cav-1, ↓Beclin-1, ↓LC3II/LC3	↓PDE5a	Oxidative stress, Apoptosis, Autophagy	[101]
	Eupatilin	In vivo(mice)	↓cTNI, ↓cTNT, ↓LDH, ↓CK-MB, ↓MDA, ↑GSH, ↓TNFα, ↓IL-1, ↓IL-6, ↓MCP-1, ↓Bax, ↑Bcl-2, ↓Caspase3	↑PI3K/AKT, ↓NF-κB	Oxidative stress, Apoptosis, Inflammation	[102]
	Luteolin	In vivo(rat)	↓BNP, ↓CK-MB, ↓TcTnT, ↓LDH, ↓MDA, ↑SOD	↓PHLPP1, ↑AKT	Oxidative stress, Apoptosis	[103]
		In vivo(mice)	↓NLRP3, ↓Caspase-1, ↓GSDM, ↓ROS, ↓apoptosis, ↑PGC-1α	↑AMPK/SIRT3/Nrf2	Oxidative stress, Apoptosis, Pyroptosis, Mitochondrial dysfunction	[104]
		In vitro(H9c2)	↑Cell viability, ↑MTP, ↓ROS, ↑SOD, ↓Bax/Bcl-2, ↓Caspase-3, ↓apoptosis	↓PI3K/AKT, ↓ERK	Oxidative stress, Apoptosis	[105]
	Diosmin	In vivo(rat)	↑HR, ↓QRS, ↓QTc, ↓CK-MB, ↓LDH, ↓cTnT, ↓IL-1β, ↓MDA, ↓Bax, ↓TNF-α, ↓HIF-1α, ↑Bcl-2	/	Oxidative stress, Apoptosis, Inflammation	[106]

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Table 1 (Continued).

Flavonoids	Compounds	StudyDesign	Marker	Signal	Mechanism	Ref.
Flavanone	Liquiritigenin	In vivo(rat)	↓LVESD, ↓LVEDP, ↑LVSP, ↑EF, ↑FS, ↓LDH, ↓BNP	↑ARHGAP18, ↓RhoA/ROCK1	Oxidative stress, Apoptosis	[107]
		In vitro(H9c2)	↑Cell viability, ↓ROS			
		In vivo(mice)	↓CK, ↓CK-MB, ↓ANP, ↓BNP, ↓cTnT, ↓ROS, ↓MDA, ↑SOD, ↓IL-1β, ↓IL-6, ↓TNF-α, ↓Bax, ↑Bcl-2, ↓Caspase-3	↓MAPK/NF-κB	Oxidative stress, Apoptosis, Inflammation	[108]
	Naringin	In vivo(rat)	↓MDA, ↑GSH, ↑SOD, ↑CAT, ↑Mitochondrial dysfunction complexes IV	/	Oxidative stress, Mitochondrial dysfunction	[109]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↑MMP, ↓cleaved Caspase-3	↓p38 MAPK	Oxidative stress	[110]
	Hesperidin	In vivo(rat)	↓TroponinI, ↓CK-Total, ↓CK-MB, ↓LDH, ↓AST, ↑GPx, ↑CAT, ↑SOD, ↓IFN-γ, ↓IL-1β, ↓TNF-α	/	Oxidative stress, Apoptosis, Inflammation	[111]
		In vivo(rat)	↓LDH, ↓CK, ↓NO, ↓TBARS, ↑SOD, ↑GSH, ↓iNOS	/	Oxidative stress	[112]
		In vivo(rat)	↓CK-MB, ↓cTnI, ↓MDA, ↓Caspase-3, ↑CAT, ↑SOD	/	Oxidative stress, Apoptosis	[113]
		In vivo(rat)	↓MDA, ↓Caspase-3, ↓apoptosis, ↑GSH	↓NF-κB, ↓p38 MAPK	Oxidative stress, Apoptosis	[114]
	Silibinin	In vitro(AC16)	↑Cell viability, ↓LDH, ↓ROS	↑IL6ST/JAK2/STAT3	Oxidative stress, Autophagy	[115]
	Naringenin	In vivo(mice)	↓LDH, ↓creatinine, ↓TnT, ↓ALT, ↓AST, ↓MDA, ↑SOD, ↑GPx, ↑CAT	/	Oxidative stress, Apoptosis	[116]
		In vivo(rat)	↓LDH, ↓CTnT, ↓MDA, ↑SOD, ↑GPx, ↑CAT, ↓TGF-β1, ↓TNF-α, ↓IL-6	/	Oxidative stress, Inflammation	[117]
		In vivo(rat)	↓LDH, ↓CPK, ↓MDA, ↓NO, ↑SOD, ↑CAT, ↑GSH, ↑GST	/	Oxidative stress	[118]
		In vitro(H9c2)	↑Cell viability, ↑Bcl-2, ↓Caspase-3/9, ↑HO-1	/	Apoptosis	[119]
		In vitro(H9c2)	↑Cell viability, ↑SOD, ↑GSH, ↑Nrf2, ↑CAT, ↓MDA	↑ERK1/2	Oxidative stress, Apoptosis	[120]
	7-hydroxyflavanone	In vitro(H9c2)	↓ROS, ↓MDA, ↓IL-6, ↑GSH/GSSG, ↑SOD, ↑ATP, ↑MMP, ↓Caspase3/7, ↑Beclin-1, ↑PGC1-α	↑AMPK, ↑PI3K/AKT, ↓mTOR	Oxidative stress, Mitochondrial dysfunction, Apoptosis, Autophagy	[121]
Chalcone	LicochalconeA	In vivo(mice)	↓LDH, ↓CK, ↓CK-MB, ↑SOD	↓PI3K/AKT/MDM2/P53	Oxidative stress, Ferroptosis	[122]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓MDA, ↑GSH/GSSG, ↓Fe^{2}□, ↑SLC7A11, ↑GPX4			
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓MDA, ↑SOD, ↑MMP	↑PI3K/AKT/Nrf2	Oxidative stress, Mitochondrial dysfunction	[123]
	Aspalathin	In vitro(H9c2)	↓ROS, ↓MDA, ↑CAT, ↑SOD, ↑ΔΨm	/	Oxidative stress, Mitochondrial dysfunction, Apoptosis	[124]
		In vitro(H9c2)	↑ATP, ↑LC3-II, ↑Bcl-2/Bax, ↓p62, ↓Caspase-3/7	↑AMPK, ↓mTOR/P53	Autophagy, Apoptosis	[125]
	Cardamonin	In vivo(mice)	↑HO1, ↑NQO1, ↑SOD, ↑GSH, ↑CAT, ↓MDA, ↓ROS, ↓Caspase-3	↑Nrf2	Oxidative stress, Inflammation	[126]
		In vivo(mice)	↑LVEF, ↑LVFS, ↑GSH/GSSG, ↓CKMB, ↓LDH, ↓c-TnT, ↑SOD, ↑GPx, ↓MDA, ↓TNF-α, ↓IL-1β, ↓IL-18, ↓IL-6, ↓TGF-β1, ↓α-SMA	↑Nrf2	Oxidative stress, Apoptosis, Inflammation, Fibrosis	[127]
		In vitro(H9c2/HL-1)	↑Cell viability, ↑GPx, ↑GSH/GSSG, ↓ROS, ↓MDA, ↓LDH, ↑HO-1, ↑NQO1, ↑GCLM↓Caspase-3, ↑Bcl-2/Bax, ↓TNF-α, ↓IL-1β, ↓IL-18, ↓IL-6			

Flavonol	Galangin	In vivo(mice)	↑LVEF, ↑LVFS, ↑GSH/GSSG, ↓CKMB, ↓LDH, ↓ROS, ↓NADPH, ↓c-TnT, ↑SOD, ↑GPx, ↓MDA, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓BNP	↑Nrf2/HO-1	Oxidative stress, Apoptosis, Inflammation, Fibrosis	[128]
		In vivo(mice)	↑LVEF, ↓cTnT, ↓CKMB, ↓LDH, ↓AST, ↓Fe^{2}□, ↓MDA, ↑GSH, ↑GPX4, ↑Nrf2, ↑Fpn, ↑Slc7a11	↑GSTP1, ↓JNK	Oxidative stress, Ferroptosis,	[129]
		In vitro(H9c2)	↑Cell viability, ↓LDH, ↓Fe^{2}□, ↓ROS, ↓Ptgs2, ↑GPX4, ↑Nrf2, ↑Fpn, ↑Slc7a11			
	Morin	In vivo(rat)	↓MDA, ↑GSH, ↑SOD, ↑CAT, ↑GPx, ↓LDH, ↓cTn-I↓CK-MB, ↓TNF-α, ↓IL-1β, ↑Bcl-2, ↑AChE	↓NF-κB	Oxidative stress, Inflammation, Apoptosis	[130]
	Myricitrin	In vivo(rat)	↓LDH, ↓CK, ↓AST, ↓ROS, ↑SOD, ↑CAT, ↑GSH-Px, ↓MDA, ↑Δψm, ↓Cytochrome C, ↓Caspase-3/9, ↑Bcl-2/Bax	↓ERK1/2/P53, ↓JNK	Oxidative stress, Apoptosis	[131]
		In vitro(H9c2)	↑Cell viability, ↓LDH, ↓ROS, ↑SOD, ↑CAT, ↑GSH-Px, ↓MDA, ↑Δψm, ↓Cytochrome C, ↓Caspase-3/9, ↑Bcl-2/Bax			
	Quercetin	In vivo(mice)	↑SOD, ↑GSH-Px, ↓MDA	/	Oxidative stress	[132]
		In vitro(H9c2)	↑Cell viability, ↓Caspase-3/9, ↑F-actin, ↓GRP78, ↓HSP60, ↓Peroxiredoxin 6	/	Oxidative stress, Inflammation, Apoptosis	[133]
		In vitro(H9c2)	↑Cell viability, ↓LDH, ↓ROS, ↑SOD, ↑CAT, ↑GPx, ↓MDA, ↑GSH, ↑MMP, ↓mPTP	↑14-3-3γ	Oxidative stress, Mitochondrial dysfunction	[134]
		In vivo(mice)	↑QCT, ↓CK, ↓LDH, ↑SOD, ↓ROS	/	Oxidative stress, Apoptosis, Mitochondrial dysfunction, Inflammation	[135]
		In vitro(H9c2)	↓ROS, ↓Bid, ↓Nox1, ↓p47, ↑Bcl-2, ↑Bmi-1, ↓p53			
		In vivo(rat)	↓CK-MB, ↓CPK, ↓Troponin, ↓LDH, ↓MDA, ↑CAT, ↑SOD, ↑PPARa, ↑PGC-1a	↓AMPK	Oxidative stress	[136]
		In vivo(rat)	↓BW, ↓SBP, ↓HR, ↓MMP-2, ↑SOD, ↑Cx-43	↑PI3K/AKT	Oxidative stress, Apoptosis	[137]
		In vivo(rat)	↓LDH, ↓CK-MB, ↓MDA, ↓NO, ↑CAT, ↑SOD, ↓TNF-α	↓AT1R/AngII	Oxidative stress, Inflammation	[138]
		In vivo(mice)	↓NO, ↓iNOS, ↑SOD, ↓MDA, ↓LDH, ↓p53	/	Oxidative stress, Apoptosis	[139]
		In vivo(rat)	↓LDH, ↓TC, ↓TG, ↓VLDL, ↓LDL, ↓MDA, ↓cTnT, ↑HDL, ↑CAT, ↑GSH, ↑SOD, ↓NO, ↓CK-MB	↓RAS/AngII	Oxidative stress, Inflammation, Apoptosis	[140]
		In vivo(mice)	↓AST, ↓ALT, ↓CK	/	Oxidative stress, Apoptosis	[141]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓Caspase3/7			
	Fisetin	In vivo(rat)	↑LVEF, ↑LVFS, ↓LVIDd, ↓LVIDs, ↓LDH, ↓CK, ↓CK-MB, ↓AST, ↑SOD, ↑CAT, ↑GPx, ↑GSH, ↑Bcl-2/Bax, ↓Caspase-3/9	↑ER(α/-β) /CHIP/SIRT1, ↓IGF-IIR	Oxidative stress, Apoptosis	[142]
		In vitro(H9c2)	↑Cell viability, ↑Bcl-2/Bax, ↑SOD2, ↓p-NF-κB, ↓Caspase-3/9			
		In vivo(rat)	↓CK-MB, ↓LDH, ↓AST, ↓ALT, ↓ALP, ↓BNP, ↓Caspase-3, ↓cTn-I, ↓TNF-α, ↓IL-1β, ↓MDA, ↓NO, ↑SOD, ↑GSH, ↓COX-II, ↓iNOs	/	Oxidative stress, Inflammation, Apoptosis	[143]

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Table 1 (Continued).

Flavonoids	Compounds	StudyDesign	Marker	Signal	Mechanism	Ref.
	Rutin	In vivo(mice)	↑LVEF, ↑LVFS, ↑Bcl-2, ↓HW/BW, ↓apoptosis, ↓fibrosis, ↓LC3II, ↓ATG5, ↓P62, ↓Caspase-3	↑PI3K/AKT	Oxidative stress, Apoptosis, Autophagy	[144]
		In vitro(H9c2)	↓LC3II, ↓ATG5, ↓P62, ↓Caspase-3, ↑Bcl-2			
		In vivo(rat)	↑LVSP, ↓LVEDP, ↑±dp/dtmax	↑miR-22-5p, ↓RAP1/ERK	Oxidative stress, Apoptosis	[145]
		In vitro(H9c2)	↓apoptosis, ↓ROS			
		In vitro(HL-1)	↑Cell viability, ↓ROS, ↓p21, ↓cleaved Caspase-3/9, ↓Bax/Bcl-2	↓miR-125b-1-3p, ↑JunD	Oxidative stress, Apoptosis	[146]
		In vivo(mice)	↑LVFS, ↑LVEF, ↑ROS1, ↑TRX, ↑PRX1, ↓HIF-1α, ↓cleaved Caspase-3/9, ↓Bax/Bcl-2	↑PI3K/AKT/mTOR	Oxidative stress, Apoptosis	[147]
	Kaempferol	In vivo(rat)	↑SOD, ↑CAT, ↓LDH, ↓Δψm, ↓Cytochrome C, ↓Caspase-3, ↓PARP, ↓p53, ↓Bax, ↑Bcl-2	↓ERK	Oxidative stress, Apoptosis	[148]
		In vitro(H9c2)	↑Cell viability, ↓apoptosis, ↓Δψm, ↓Cytochrome C, ↓Caspase-3, ↓PARP, ↓p53, ↓Bax, ↑Bcl-2			
	Robin	In vivo(rat)	↑SOD, ↑CAT, ↑GPx, ↑GRd, ↓LDH, ↓CPK, ↓SGOT, ↓SGPT, ↓ROS, ↓TBARS, ↓COX-2, ↓LOX-15, ↓p53, ↓Bax, ↑Bcl-2	↓TGF-β1	Oxidative stress, Inflammation	[149]
		In vitro(H9c2)	↑Cell viability, ↑CAT, ↑SOD, ↑GST↓MDA, ↓LDH, ↓ROS, ↓Caspase-3/9	↓PERK/ATF-6	Oxidative stress, Apoptosis	[150]
	Isorhamnetin	In vivo(rat)	↓LDH, ↓AST, ↓CK	↓JNK, ↓ERK1/2, ↓p38 MAPK	Oxidative stress, Apoptosis, Mitochondrial dysfunction	[151]
		In vitro(H9c2)	↑Cell viability, ↓LDH, ↓ROS, ↑SOD, ↑CAT, ↑GSH-GPx, ↓MDA, ↓Caspase-3, ↓Bax, ↑Bcl-2			
Anthocyanin	Cyanidin 3-glucoside	In vitro(H9c2)	↑Cell viability	/	Oxidative stress	[152]
		In vivo(mice)	↑Cell viability, ↓LDH, ↓ROS, ↓ONOO□, ↓O_2□, ↓H_2O_2, ↓NO	↓RAS	Oxidative stress, Inflammation	[153]
		In vitro(HL-1)	↑Cell viability, ↓ROS			
	Cyanidin chloride	In vivo(mice)	↓LDH, ↓CK-MB, ↓Fe^2□	↑Nrf2	Ferroptosis, Apoptosis	[154]
		In vitro(H9c2)	↑Cell viability, ↑ATP, ↓ROS, ↓ONOO□, ↑GPX4			
Flavanol	Catechin	In vivo(rat)	↓CK, ↓CK-MB, ↓LDH, ↓MDA, ↓H_2O_2, ↓NO, ↑SOD, ↑GSH, ↑GST, ↑CAT	/	Oxidative stress, Apoptosis	[155]
		In vivo(rat)	↓MDA, ↓TroponinI, ↓iNOS, ↑GSH-Px, ↑CAT, ↑SOD, ↓TNF-α	↓NF-κB	Oxidative stress, Inflammation	[156]
	(-)-Epigallocatechin-3-gallate	In vivo(mice)	↓LDH, ↓ROS, ↓Δψm, ↑MnSOD, ↓Ca^2□	/	Oxidative stress, Apoptosis, Calcium dys-homeostasis	[157]
		In vitro(H9c2)	↑Cell viability, ↓ROS, ↓apoptosis, ↑CTA, ↑+dl/dt, ↑-dl/dt, ↓Ca^2□	/	Oxidative stress, Apoptosis, Calcium dys-homeostasis	[158]
		In vitro(H9c2)	↑Cell viability, ↓apoptosis, ↓LDH, ↓ROS, ↓MDA, ↑MnSOD, ↑CTA, ↑GPx	/	Oxidative stress, Apoptosis	[159]
		In vivo(rat)	↓CK-MB, ↓LDH, ↓QTc, ↓Caspase-3/12, ↓calpain2, ↓p53, ↓Hsp70	↑ErbB2, ↓NF-κB	Oxidative stress, Apoptosis, Inflammation	[160]

cardiomyoblast cells and reduced DOX-induced apoptosis by modulating the PI3K/Akt signaling pathway and regulating the expression of Bcl-2 and Bax proteins. Additionally, calycosin alleviated oxidative stress in H9c2 cells and mouse models by enhancing the activities of key antioxidant enzymes such as glutathione peroxidase (GPx), CAT, and SOD. It also decreased oxidative damage markers, including malondialdehyde (MDA), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST). Mechanistically, calycosin exerted its effects through the Sirt1-Nlrp3 pathway, as shown by the suppression of Nlrp3 inflammasome activation and Txnip expression. Inhibition of Sirt1 using Ex527 attenuated the protective effects of calycosin, confirming its role in this pathway.[70] A second study utilized zebrafish embryo-adult models for rapid pharmacological screening and in vitro analyses to elucidate calycosin's gene-specific mechanisms on chronic DIC. In adult zebrafish with late-onset DIC, calycosin treatment, initiated 28 days post-DOX injection, restored cardiac function and autophagic activity, which were severely impaired by DOX. Dysregulated autophagy, a key pathological feature of DIC, was ameliorated by calycosin through the activation of autophagy related 7 (Atg7), an E1-like activating enzyme essential for autophagy, suggesting the cardioprotective role of calycosin by modulating autophagy.[71]

Ononin

Ononin, an isoflavone glycoside found in sources like Ononis soybean, *Glycyrrhiza uralensis*, red clover, and other herbs, has shown promising medicinal properties.[168] Recent studies highlight its anti-inflammatory, antitumor, antidiabetic, antioxidant, antiobesity, antiviral, cardioprotective, and neuroprotective effects.[169] Ononin has shown promising cardioprotective effects against DIC by modulating apoptosis and endoplasmic reticulum stress through the Sirt3 pathway. This study employed both in vitro and in vivo models to investigate the underlying mechanisms. In vivo experiments involved DOX-induced cardiomyopathy in Wistar rats, where ononin was administered intragastrically two weeks prior to DOX treatment. Echocardiographic analysis demonstrated that ononin improved cardiac function by increasing LVEF and left ventricular systolic fractional shortening (LVFS). In vitro studies using DOX-treated H9c2 cardiomyoblast cells further corroborated these findings, showing that ononin significantly mitigated DOX-induced apoptosis and ER stress. Mechanistically, ononin reduced the Bax/Bcl-2 ratio and suppressed the expression of endoplasmic reticulum stress markers, including Grp78 and Chop. These effects were linked to the activation of Sirt3, as the use of a Sirt3 inhibitor (3-TYP) attenuated the protective effects of ononin, confirming its dependence on the Sirt3 pathway.[72]

8-Formylophiopogonanone B

8-Formylophiopogonanone B (8-FOB), a natural isoflavone derived from the root tubers of *Ophiopogon japonicus*, has demonstrated antitumor, hepatoprotective as well as cardioprotective effects against DIC.[73,74,170] In the previous study, Qin et al employed a mouse model of acute cardiotoxicity and bioinformatics analyses to elucidate the mechanisms underlying DOX-induced cardiac damage and the protective role of 8-FOB. The in vivo experiments involved C57BL/6J mice revealed that 8-FOB administration effectively mitigated DOX-induced cardiac injury and dysfunction. These protective effects were closely associated with the downregulation of Hmox1, a hub gene identified through bioinformatics analysis and which acted as a key mediator of DIC. Mechanistically, Hmox1 expression was significantly upregulated in DOX-treated hearts, promoting myocardial inflammation and fibrosis. 8-FOB treatment inhibited Hmox1 expression, thereby reducing these pathological processes and preserving cardiac function.[74]

Genistein

Genistein (4′,5,7-trihydroxyisoflavone), a key nutraceutical molecule in soybeans, is a phytoestrogen with various pharmacological effects in animal cells. Since firstly isolated from the brooming plant *Genista tinctoria*, genistein is found widely distributed in the Fabaceae family and exerts estrogen-like functions.[171] Preclinical studies have shown genistein's antioxidant, anti-aging, anti-inflammatory, antitumor, antibacterial, antiviral, neuroprotective and potential benefits for angiogenesis, estrogenic activity, diabetes, and lipid metabolism.[172] Genistein has been shown to mitigate DIC through multiple molecular mechanisms. Two studies utilizing both in vivo and in vitro models provide compelling evidence for genistein's efficacy in reducing oxidative stress, inflammation, apoptosis, and autophagy in DOX-treated hearts. In the first study, male Sprague-Dawley rats pre-treated with genistein demonstrated improved cardiac function and reduced pathological remodeling following DOX administration. Genistein significantly inhibited Erk1/2

phosphorylation while upregulating Stat3 and c-Myc expression. This modulation of the Erk/Stat3/c-Myc pathway contributed to reduced cardiomyocyte apoptosis and autophagy, as evidenced by molecular docking analysis and the use of a Mek1/2 inhibitor (U0126), which mimicked genistein's effects. Immunohistochemistry and electron microscopy revealed structural preservation in genistein-treated hearts, correlating with improved clinical cardiac function.[75] The second study further elucidated genistein's cardioprotective mechanisms, highlighting its ability to modulate redox and apoptotic pathways. In a mouse model, genistein treatment significantly reduced serum cardiac troponin levels and markers of oxidative stress, including ROS, lipid peroxidation (LPO), and 4-hydroxynonenal-protein adducts (HNE). Genistein also attenuated inflammatory responses by downregulating pro-inflammatory cytokines (TNF-α, IL-6, IL-8). Importantly, genistein activated the Nrf2/Hmox1 antioxidant signaling pathway, enhancing cellular defense mechanisms. Concurrently, it restored survival proteins such as p-Akt and Bcl-2 while suppressing pro-apoptotic markers, including Bax and cleaved Caspase-3.[76]

Puerarin

Puerarin (Pue) is a C-glucoside of the isoflavone daidzein extracted from *Pueraria lobata* (Willd). Ohwi, which is well known as Gegen (Chinese name) in TCM.[173] Puerarin's broad range of pharmacological properties, including vasodilation, cardioprotection, neuroprotection, antioxidant, anti-tumor, anti-inflammatory effects, pain relief, bone formation promotion, alcohol intake inhibition, and reduction of insulin resistance, may underlie its diverse medicinal benefits.[174] Puerarin has shown significant cardioprotective effects against DIC through its modulation of oxidative stress, mitochondrial function, and autophagy pathways. This study investigated the mechanisms by which Pue pretreatment protects myocardial cells and tissue from DOX-induced damage using both in vivo and in vitro models. In adult mice and H9c2 cardiomyoblast cells, Pue pretreatment enhanced cell viability, reduced LDH activity, and decreased apoptosis levels. Pue also mitigated excessive oxidative stress, preserved mitochondrial function and energy metabolism, and improved overall myocardial function. These effects were associated with the upregulation of 14-3-3γ protein expression and its interaction with PKCε. This interaction facilitated the phosphorylation and translocation of PKCε to mitochondria, which subsequently activated adaptive autophagy, an essential mechanism for cardioprotection. However, the cardioprotective effects of Pue were weaken by the inhibition of 14-3-3γ expression, PKCε activity, or autophagy (using 3-methyladenine), demonstrating the critical role of the 14-3-3γ/PKCε pathway in mediating adaptive autophagy and myocardial protection.[77]

Irigenin

Irigenin (IR), an isoflavonoid compound derived from the rhizome of *Belamcanda chinensis*, has shown antioxidative, anti-inflammatory and anti-tumor activity,[175] but also has promising cardioprotective effects against DIC through the modulation of apoptosis, oxidative stress, and inflammation.[78] This study utilized both in vivo and in vitro models to explore the underlying mechanisms, focusing on the regulatory role of miR-425 and its target, receptor interacting serine/threonine kinase 1 (Ripk1). In DIC models, IR significantly attenuated cardiac fibrosis, dysfunction, and injury. It reduced apoptosis, ROS accumulation, and inflammatory responses in heart tissue and HL-1 cells. Mechanistically, DOX treatment resulted in a substantial decrease in miR-425 levels, which was rescued by IR. miR-425 directly targeted Ripk1, a key mediator of cardiomyocyte injury, and IR effectively suppressed the DOX-induced overexpression of Ripk1 both in vivo and in vitro. Further experiments demonstrated that transfection with a miR-425 mimic inhibited Ripk1 expression, reducing apoptosis, oxidative stress, and inflammation in DOX-exposed cells. Conversely, miR-425 inhibition increased Ripk1 expression and exacerbated cardiomyocyte injury. Importantly, Ripk1 knockdown mirrored the protective effects of miR-425 overexpression, whereas Ripk1 overexpression negated these benefits, underscoring the critical role of the miR-425/Ripk1 axis in DIC.[78]

Flavones

Baicalin

Baicalin (7-D-glucuronic acid-5,6-dihydroxyflavone) belongs to the natural flavone extracted from the roots of *Scutellaria baicalensis*, exhibiting anti-inflammatory, antiviral, antitumor, antibacterial, anticonvulsant, antioxidant,

hepatoprotective, and neuroprotective properties.[79] Involving these pharmacological effects, the plant was widely used for treatment of various diseases including nervous system disorders (Alzheimer's disease, Parkinson's disease, and depression), metabolic disorders (obesity-related diseases), intestinal disorders (inflammatory bowel disease and dysbiosis) and cancers in TCM.[176] Baicalin (BA) has demonstrated significant cardioprotective effects against DIC by targeting oxidative stress, inflammation, and ferroptosis pathways. Two studies provide insights into its mechanisms of action and therapeutic potential. In the first study, BA was delivered using angiotensin II receptor type 1 (AT1R)-targeted supramolecular nanofibers to selectively inhibit ferroptosis, an iron-dependent form of cell death implicated in DOX-induced cardiomyopathy. In vitro, BA delivery attenuated peroxide accumulation and suppressed ferroptosis in cardiomyocytes. In a murine model, targeted BA delivery achieved superior cardiac accumulation and therapeutic outcomes compared to systemic administration, effectively reducing cardiomyocyte death and preserving myocardial function.[80] The second study focused on BA's anti-inflammatory and antioxidant effects in a DIC model in Swiss albino mice. BA pretreatment significantly prevented DOX-induced elevations in serum cardiac biomarkers, such as cardiac Troponin-I (cTnI) and lactate dehydrogenase, and mitigated histopathological cardiac damage. Mechanistically, BA suppressed toll-like receptor 4 (TLR4) overexpression, subsequently inhibiting NF-κB and IL-1β pathways, which are critical mediators of DOX-induced inflammation. Additionally, BA reversed DOX-induced oxidative stress by reducing MDA and restoring GSH levels. BA also activated the Wnt/β-catenin pathway by suppressing dickkopf WNT signaling pathway inhibitor 1 (Dkk1), further contributing to its cardioprotective effects.[81]

Baicalein

Baicalein, a natural flavone extracted from the dried roots of *Scutellaria baicalensis* (S. baicalensis) Georgi (common name: Huangqin in China) which has been widely employed for many centuries in traditional Chinese herbal medicine as popular antibacterial and antiviral agents.[177] Following years of research, the pharmacological activities of baicalein were further uncovered, including anti-tumor, antidiabetic, antimicrobial, antiaging, neuroprotective, respiratory protective, gastroprotective, hepatic protective, and renal protective effects.[178] Of note, baicalein was found to be a strong free radical scavenger and xanthine oxidase inhibitor, enhancing endothelial function and providing cardiovascular protection against cell damage caused by oxidative stress.[177] Baicalein has demonstrated significant cardioprotective effects against DIC by mitigating oxidative stress, apoptosis, and inflammation without compromising DOX's anti-tumor efficacy. Two studies elucidate its mechanisms of action using both in vitro and in vivo models. In vitro, baicalein significantly reduced DOX-induced cardiomyocyte death in a chick cardiomyocyte model by attenuating ROS generation and preserving mitochondrial membrane potential. Baicalein decreased DNA fragmentation and inhibited the phosphorylation of the pro-apoptotic kinase JNK, a critical mediator of ROS-induced apoptosis. Co-treatment of cardiomyocytes with DOX and JNK inhibitor SP600125 also reduced JNK phosphorylation and enhanced cell survival, demonstrating that its protective effects are mediated via JNK signaling inhibition. Importantly, baicalein did not interfere with DOX's antiproliferative effects against breast cancer MCF-7 cells, preserving its chemotherapeutic efficacy.[82] In vivo, oral administration of baicalein significantly reduced serum markers of cardiac injury in BALB/c mice, including CK-MB, LDH, AST, and ALT, and ameliorated histopathological damage in the heart. Baicalein restored myocardial antioxidant defenses by upregulating Nrf2 and Hmox1 expression, thereby reducing oxidative stress. Additionally, it reversed the Bax/Bcl-2 ratio and suppressed the expression of p53, cleaved Caspase-3, and Parp, preventing apoptosis and DNA damage. Baicalein also inhibited DOX-induced NF-κB activation by suppressing IκBα phosphorylation and nuclear translocation of the p65 subunit, reducing inflammatory signaling. Elevated iNOS and NO levels in DOX-treated mice were significantly decreased by baicalein, further confirming its anti-inflammatory effects.[83]

Isoorientin

Isoorientin (ISO), a natural tetrahydroxyflavone and C-glycoside flavone found in herbs like *Lophatherum gracile* and *Patrinia scabiosaefolia*, exhibits various medicinal effects, including antibacterial, anti-inflammatory, and anti-tumor properties.[179] Its strong antioxidant and anti-inflammatory activities have shown promise in addressing metabolic complications such as hyperglycemia, hyperlipidemia, and insulin resistance.[180] ISO has also potential cardioprotective effects against DIC while enhancing the chemotherapeutic efficacy of DOX. The dual role of ISO in improving

antiproliferation against tumor cell and protecting cardiomyocytes from DOX-induced damage was investigated using both in vitro and in vivo models. In vitro, ISO synergistically enhanced the antiproliferative effects of DOX on various tumor cell lines, including Hela, HepG2, HT-29, and A549 cells. Simultaneously, ISO significantly improved the survival rate of DOX-injured H9c2 cardiomyocytes by reducing ROS, maintaining mitochondrial integrity, and inhibiting apoptosis. These protective effects were further validated in a mouse model of DIC, where ISO improved survival, preserved cardiac function, and reduced myocardial injury, as demonstrated by improved electrocardiogram (ECG) profiles, myocardial enzyme levels, and histopathological analysis. Mechanistically, ISO exerted its dose-dependent cardioprotective effects through the inhibition of the MAPK and Caspase-dependent apoptosis pathways. Proteomics and pharmacological network analyses identified several key targets, including Caspase-3, EGFR, MAPK1, and Stat3. Further analysis revealed that ISO upregulated Nrf2 and TGF-β3 expression by downregulating the phosphorylation of JNK and p38 proteins in the MAPK pathway and suppressing Akt and Stat3 expression. Furthermore, ISO reduced cleaved Caspase-3 levels and increased Bcl-xL expression, confirming its inhibition of apoptosis in DIC.[84]

Vaccarin

Vaccarin is a kind of natural flavonoid glycoside which belongs to flavones and is found in the seeds of a Chinese herbal *Vaccaria hispanica* (Mill).[181] Vaccarin possesses a multitude of pharmacological activities, including antioxidation, anti-inflammatory, antidiabetic and neuroprotective effects.[182] Vaccarin has demonstrated significant cardioprotective effects against DIC by targeting oxidative stress and apoptosis pathways. This study explored vaccarin's therapeutic potential in both in vivo and in vitro models, revealing its ability to mitigate cardiac dysfunction and cellular damage caused by DOX. In a mouse model, vaccarin effectively ameliorated DOX-induced cardiac dysfunction, reducing oxidative stress and preventing apoptosis. Mechanistically, vaccarin inhibited the activation of the p38 MAPK pathway, a key mediator of ROS-induced myocardial injury. In vitro studies using H9c2 cardiomyoblast cells further supported these findings, showing that vaccarin alleviated mitochondrial membrane depolarization and reduced ROS generation induced by DOX. However, the protective effects of vaccarin were reversed by anisomycin, a p38 MAPK agonist, confirming the role of this pathway in mediating its cardioprotective effects.[85]

Chrysin

Chrysin (5,7-dihydroxyflavone) which is categorized under the class of flavones occurs naturally in many plants, such as propolis, honey, passion fruit, and even in mushrooms and other plant sources.[183] In general, chrysin exhibits many biological activities and pharmacological effects, including antioxidant, anti-inflammatory, anti-tumor, and antiviral activities.[184] Chrysin has shown significant cardioprotective effects against chronic DIC in a rat model. The study elucidates the mechanisms underlying its protective effects, highlighting its role in mitigating oxidative stress, apoptosis, and inflammatory signaling while enhancing cardioprotective pathways. Male Sprague-Dawley rats were treated with DOX and/or chrysin for four weeks. Chrysin effectively prevented DOX-induced cardiomyopathy, evidenced by normalization of conduction abnormalities, reductions in serum CK-MB and LDH levels, and attenuation of histopathological cardiac damage. It also ameliorated oxidative stress by decreasing lipid peroxidation and upregulating antioxidant enzymes, restoring the redox balance disrupted by DOX. Mechanistically, chrysin inhibited DOX-induced activation of the p53-dependent apoptotic pathway by downregulating P53, Bax, Puma, Noxa, Cytochrome c, and Caspase-3, while upregulating the anti-apoptotic protein Bcl-2. Furthermore, chrysin suppressed the activation of MAPK, including p38 and JNK, and inhibited NF-κB signaling. These pathways are critical mediators of DOX-induced apoptosis and inflammation. Additionally, chrysin restored the VEGF/Akt pathway, which was suppressed by DOX. By decreasing PTEN expression and increasing VEGF and Akt levels, chrysin enhanced survival signaling in cardiomyocytes. This comprehensive modulation of apoptotic, inflammatory, and oxidative stress pathways underscores chrysin's cardioprotective efficacy.[86]

Jaceosidin

Jaceosidin, a flavonoid compound found in several species of Artemisia, has garnered increasing attention for its potential therapeutic effects in cardiovascular diseases.[185] Recent studies have highlighted its antioxidant, anti-inflammatory, antitumor and anti-apoptotic properties,[186] which may offer protection against various forms of cardiac injury.

One of the primary areas of focus has been its role in mitigating DIC. In an acute DIC model, jaceosidin orally administered was found to dose-dependently reduced oxidative stress, inflammation, and cardiomyocyte loss induced by DOX. Jaceosidin effectively inhibited myocardial oxidative damage and attenuated the inflammatory response, thereby preventing myocardial apoptotic death. These effects collectively improved cardiac function in mice exposed to DOX. Mechanistically, jaceosidin's protective effects were mediated by the activation of Sirt1 signaling pathway. Jaceosidin enhanced Sirt1 activity, which played a crucial role in mitigating oxidative stress and apoptosis. However, in Sirt1-deficient cardiomyocytes and mice, the cardioprotective effects of jaceosidin were abrogated, confirming the essential role of Sirt1 activation in its mechanism of action.[87]

Chrysoeriol

Chrysoeriol is an active flavone compound derived from the Chinese medicinal herb *Lonicerae japonicae flos* in the dried flower bud or bloomed flower of *Lonicera japonica* Thunberg.[187] The pharmacological properties including antitumor, anti-inflammatory, antibacterial, antifungal, anti-osteoporosis, anti-insecticide, and neuroprotective actions have been shown in a number of studies, showing its promising potential to prevent or treat diseases including cancer, diabetes, inflammation, osteoporosis, Parkinson's disease, and cardiovascular diseases.[188] Chrysoeriol has demonstrated cardioprotective potential against DIC by mitigating apoptosis and oxidative stress in H9c2 cells without compromising DOX's antitumor efficacy. The study explored its effects and underlying mechanisms using a series of biochemical and cellular assays. Chrysoeriol significantly reduced DOX-induced apoptosis and cell death in H9c2 cells and LDH release measurements. At a dose of 20 μg/mL, chrysoeriol effectively decreased intracellular ROS levels and MDA concentrations while restoring the activities of critical antioxidant enzymes, such as SOD and GPx, to their normal levels. These findings suggest that chrysoeriol protects cardiomyocytes by neutralizing oxidative stress and enhancing cellular antioxidant defenses. Importantly, further analysis confirmed that the addition of chrysoeriol did not interfere with DOX's antitumor activity, as demonstrated in HeLa cell models. This indicates that chrysoeriol selectively mitigates the cardiotoxic side effects of DOX without diminishing its chemotherapeutic efficacy.[88]

Pinocembrin

Pinocembrin (PCB, 5,7-dihydroxyflavone), a flavonoid compound derived from fungi and hive products, mainly honey and propolis, exhibits a wide range of biological activities, including anti-inflammatory, antioxidant, antimicrobial, neuroprotective, cardioprotective and anti-tumor activities.[189] Recent studies have highlighted PCB's cardioprotective effects against various forms of heart damage, including ischemia-reperfusion injury, heart failure and DIC.[190,191] In vivo, PCB administration significantly improved cardiac function impaired by DOX, as evidenced by increased LVEF and LVFS, along with reductions in left ventricular internal diameters (LVIDd, LVIDs) and myocardial fibrotic area. PCB also attenuated cardiac injury markers, such as LDH and CK-MB levels, and decreased pro-inflammatory cytokines IL-1β and IL-18, highlighting its anti-inflammatory effects. Mechanistically, PCB was shown to inhibit Nlrp3-mediated pyroptosis and oxidative stress by activating the Nrf2/Sirt3 signaling pathway in DIC. However, inhibition of Nrf2 in H9c2 cells abolished the protective effects of PCB, confirming the critical role of Nrf2/Sirt3 pathway.[89]

7,8-Dihydroxyflavone

7,8-Dihydroxyflavone (7,8-DHF), a small-molecule agonist of the TrkB receptor, has attracted attention as a therapeutic candidate for diseases involving the BDNF pathway in recent years. While its potential in neurological disorders is well-documented, its role in cardiac diseases remains less understood. In the context of DIC, 7,8-DHF has demonstrated significant cardioprotective effects in both in vivo and in vitro models. Specifically, 7,8-DHF significantly improved cell viability, reduced cell death, and enhanced mitochondrial respiration, membrane potential, and the expression of OPA1 protein in H9c2 cells. In a DIC mouse model, 7,8-DHF improved cardiac function and reduced cardiac injury. Mechanistically, 7,8-DHF restored the expression of Ampk and Stat3 and modulated signaling pathways by activating Akt phosphorylation and reducing Erk activity. The protective effects were abolished by ANA-12, a TrkB antagonist, confirming the involvement of TrkB activation. Furthermore, the regulatory effects of 7,8-DHF on Stat3 and Ampk were dependent on Akt signaling, as they were reversed by an Akt inhibitor.[90]

Oroxylin A

Oroxylin A (5′7-dihydroxy-6-methoxy-2-phenyl-4H-1-benzopyran-4-one) is a monomethoxy and dihydroxy flavone, and is mainly found in the root-bark O. *indicum, S. baicalensis* (radix), *S. lateriflora, Anchietea pyrifolia*, and *Aster himalaicus*, which are used extensively in Ayurveda and TCM.[192,193] A plethora of studies have reported that oroxylin A possesses a broad spectrum of pharmacological functions including anti-bacterial, anti-viral, anti-oxidant, antiinflammatory, antitumor, anti-invasive, neuroprotective, hepatoprotective, and pro-apoptotic properties, which buttresses its promising potential in the treatment of diseases.[192,193] In a recent study, oroxylin A has demonstrated protective effects against DOX-induced acute cardiotoxicity, a critical limitation of DOX's clinical use due to its adverse impact on cardiac function. Oroxylin A was administered to mice pre- and post-DOX exposure, effectively mitigating heart weight loss, cardiac functional decline, and elevations in myocardial injury markers. Mechanistically, oroxylin A alleviated DOX-induced oxidative stress, inflammation, and myocardial apoptosis, both in vivo and in vitro. These protective effects were mediated through activation of the Sirt1 signaling pathway via the cAMP/PKA axis and were abrogated in Sirt1-deficient models.[91]

Acacetin

Acacetin is a di-hydroxyl and mono-methoxide flavone (4′-methoxy-5,7-dihydroxyflavone), which is abundantly present in various herbs used in TCM, such as snow lotus (Saussurea).[194] Literature indicates that acacetin demonstrates a wide range of pharmacological effects, including antitumor, anti-bacterial, anti-viral, antiinflammatory, neuroprotective, cardioprotective, antiobesity and hepatoprotective properties.[195] A recent study has demonstrated a significant cardioprotective effect of acacetin against DOX-induced cardiomyopathy in a mouse model, with further mechanistic insights provided using cultured rat cardiomyocytes. In vivo, acacetin effectively mitigated cardiac dysfunction and myocardial fibrosis caused by DOX, largely through the restoration of impaired Nrf2/Hmox1 and Sirt1/Ampk signaling pathways. In vitro studies revealed that DOX-induced reductions in cell viability and increases in ROS production were counteracted by acacetin in a concentration-dependent manner. These effects were mediated by the activation of Sirt1/Ampk signaling and the enhancement of antioxidative (Nrf2/Hmox1, SOD1/SOD2) and anti-apoptotic defenses. Importantly, silencing Sirt1 abolished these protective effects, underscoring the centrality of Sirt1 in the cardioprotective mechanism.[92]

Dihydromyricetin

Dihydromyricetin (DHM), a 2,3-dihydroflavonol compound, represents the principal bioactive constituent extracted from the tender stems and leaves of the Chinese medicinal plant *Ampelopsis grossedentata* (A. grossedentata), which exhibits a wide range of biological activities, including anti-alcohol intoxication, anti-inflammatory, antibacterial, antioxidant, and anti-tumor properties, as well as regulatory effects on lipid metabolism and blood glucose levels.[196] In recent years, DHM has garnered attention for its cardioprotective effects against DIC. Studies demonstrate that DHM mitigates DOX-induced cardiac injury through multiple mechanisms, offering a promising strategy for enhancing the therapeutic window of DOX without compromising its antitumor efficacy. In vivo experiments with C57BL/6 mice and in vitro studies using AC16 cardiomyocytes revealed that DHM preconditioning alleviated the inhibition of autophagy and excessive apoptosis triggered by DOX. These protective effects were mediated by the activation of the Ampk/mTOR signaling pathway, a crucial regulator of autophagy. DHM restored autophagic flux, reduced intracellular ROS levels, and inhibited oxidative stress, thereby preventing DOX-induced cardiac damage.[93] DHM also exerts anti-inflammatory effects by targeting the Nlrp3 inflammasome, a key mediator of DOX-induced cardiac inflammation. In a rat model and H9c2 cell line, DHM inhibited Caspase-1 activity and suppressed the release of pro-inflammatory cytokines IL-1β and IL-18. These effects were closely associated with the upregulation of Sirt1, a protein known for its anti-inflammatory and antioxidative properties. The inhibition of Sirt1 abolished DHM's cardioprotective effects, underscoring its pivotal role in mediating DHM's actions.[94] In addition to modulating autophagy and inflammation, DHM rescues the expression of anti-apoptotic proteins such as ARC, which are downregulated during DOX-induced myocardial injury. Restoration of ARC expression reduced myocardial cell apoptosis and prevented abnormal electrocardiographic changes. These effects were accompanied by decreases in serum markers of cardiac injury, such as ALT, LDH, and CK-MB, further highlighting DHM's protective potential. Importantly, DHM preserves DOX's anti-tumor efficacy while protecting against its cardiotoxicity.

Studies on human leukemia U937 cells and xenograft models demonstrated that DHM enhanced DOX's anti-tumor activity through a p53-dependent mechanism. This dual benefit of DHM protecting cardiac tissue while potentiating anti-tumor effects suggests that it could significantly expand the therapeutic window of DOX.[95]

Apigenin

Apigenin (4′,5,7,-trihydroxyflavone) is a natural phenolic flavone compound which is present principally as glycosylated in significant amount in vegetables (parsley, celery, onions), fruits (oranges), herbs (chamomile, thyme, oregano, basil), and plant-based beverages (tea, beer, and wine).[197] Many studies have verified apigenin's antiinflammatory, antioxidant, and anti-apoptotic activities, showcasing its therapeutic potential for diverse human diseases, such as cardiometabolic disorders, autoimmune and neurodegenerative diseases, skin inflammatory conditions and even several types of cancers.[198,199] Numerous studies have highlighted the cardioprotective effects of apigenin against DIC, primarily through the enhancement of mitochondrial function via modulation of the mitochondrial unfolded protein response (UPRmt). In a murine model, co-administration of apigenin significantly improved cardiac function, attenuated myocardial edema, suppressed inflammatory responses, and upregulated the transcription of UPRmt-related genes, thereby promoting cardiomyocyte survival. In DOX-treated HL-1 cardiomyocytes, apigenin restored ATP production, enhanced mitochondrial antioxidant capacity, and reduced apoptotic cell death. Notably, these protective effects were abrogated upon inhibition of UPRmt, underscoring its critical role in apigenin's mechanism of action. Mechanistically, apigenin prevented DOX-induced downregulation of Sirt1 and Atf5, key regulators of UPRmt, and its cardioprotective effects were abolished in Sirt1 knockout mice or following Sirt1 knockdown in vitro.[96] Additionally, apigenin has been shown to protect against DIC by inhibiting cardiomyocyte pyroptosis through the modulation of GSK-3β signaling. In both a murine model of DIC and DOX-stimulated H9c2 cells, apigenin treatment significantly reduced the expression of pyroptosis-related factors. These effects were associated with increased phosphorylation of GSK-3β and decreased activation of NF-κB p65. The protective effects of apigenin were replicated by treatment with SB216763, a GSK-3β inhibitor, whereas siRNA-mediated knockdown of GSK-3β negated the benefits of apigenin in vitro. By inhibiting GSK-3β, apigenin reduced NF-κB p65 activation, thereby attenuating inflammation and pyroptosis in both cellular and animal models.[97] Furthermore, apigenin exerts cardioprotection against DIC by improving cardiac function and mitigating cardiac injury through its anti-fibrotic, antioxidant, and anti-apoptotic properties. In a study involving male Wistar rats, apigenin administration significantly improved cardiac functional parameters, including EF, FS, LVIDs, and LVIDd. Apigenin treatment also markedly reduced serum levels of cardiac and hepatic injury markers, including LDH, CK-MB, cTnI, ALT, and AST. Additionally, apigenin attenuated cardiac fibrosis, decreased the expression of pro-apoptotic proteins (Caspase-3 and Bax), and increased the levels of the anti-apoptotic protein Bcl-2. Moreover, apigenin enhanced antioxidant defenses by significantly elevating SOD activity and reducing MDA levels, further supporting its multi-faceted cardioprotective effects.[98]

Scutellarin

Scutellarin chemically named 4,5,6-trihydroxylflavone-7-O-glucuronoside is a polyphenolic monomer flavone compound widely found in a number of herbs including *Scutellaria barbata* and *Erigeron breviscapus*.[200] Scutellarin exhibits a wide range of pharmacological properties, including antioxidant, anti-inflammatory, anti-apoptotic, antitumor and vasodilatory effects.[201] These multifaceted protective effects render scutellarin a potentially valuable agent in addressing chronic conditions such as cerebrovascular diseases, cardiovascular disorders, neurodegenerative diseases, metabolic syndromes and several types of cancer.[202] Previous studies have demonstrated that scutellarin exerts significant protective effects against DIC. In a rat model of DIC, co-administration of scutellarin significantly reduced LDH activity, MDA levels, and cTnT concentrations, while restoring LVEF and LVFS to near-normal levels compared to the DOX-treated group. Histopathological assessments further confirmed a marked reduction in cardiac tissue damage in scutellarin-treated animals. Pharmacokinetic analyses revealed that scutellarin decreased DOX accumulation in cardiac tissues without altering the plasma AUC, suggesting a cardioprotective mechanism mediated by reduced DOX exposure in the heart.[99] Additionally, scutellarin has been shown to protect against DIC by targeting oxidative stress, DNA damage, apoptosis, and autophagy through modulation of the Akt/ mTOR signaling pathway. In vitro studies using H9c2 cardiomyocytes,

cardiac fibroblasts (CFs), and human umbilical vein endothelial cells (HUVECs) demonstrated that scutellarin pretreatment significantly improved cell viability and attenuated DOX-induced mitochondrial dysfunction and apoptosis. Notably, H9c2 cells exhibited greater sensitivity to DOX compared to CFs and HUVECs. Scutellarin pretreatment dose-dependently reversed oxidative stress and mitochondrial dysfunction, while inhibiting DOX-induced Bax/Bcl-2-mediated apoptosis and autophagy activation. These findings underscore scutellarin's potential as a cardioprotective agent against DIC, primarily through its antioxidant, anti-apoptotic, and autophagy-modulating properties.[100] However, despite its multi-targeted therapeutic potential, scutellarin faces significant challenges, including low bioavailability and a paucity of robust clinical data, which currently limit its broader therapeutic application.

Icariin

Icariin, a principal bioactive flavone constituent derived from *Herba Epimedii*, demonstrates a broad spectrum of pharmacological properties, including neuroprotective, cardioprotective, antitumor, antioxidative, immunomodulatory, lipid-lowering and reproductive-enhancing effects.[203] Clinically, it has been extensively utilized for the management of various pathological conditions, such as osteoporosis, atherosclerosis, asthma, rheumatoid arthritis, diabetes mellitus, Alzheimer's disease, Parkinson's disease, and cerebral ischemia.[203,204] Pharmacokinetic investigations in rodent models have elucidated the metabolic pathways of icariin, identifying its primary metabolites as icaritin, icariside I, icariside II, and desmethylicaritin.[205] Evidence suggests that icariin and its metabolites confer significant cardioprotective benefits through multiple mechanisms, including the amelioration of inflammatory responses and oxidative stress, modulation of cellular proliferation and apoptosis, inhibition of vascular endothelial cell injury and senescence, and facilitation of stem cell differentiation and migration.[203] According to the literatures, icariin exerts its pharmacological effects through multiple molecular mechanisms, including the activation of key signaling pathways such as Akt, Ppars, and Sirt1. Additionally, it inhibits NF-κB, MAPK signaling and the subsequent production of pro-inflammatory cytokines. Furthermore, icariin has been shown to suppress PDE5 activity and modulate the hypothalamic-pituitary-adrenal (HPA) axis.[206] A previous study found that icariin exerts significant cardioprotective effects against DIC by targeting oxidative stress, mitochondrial dysfunction, and dysregulated autophagy. This is achieved through the modulation of Caveolin-1 expression and inhibition of PDE5a activity. In H9c2 cardiomyocytes, icariin treatment markedly enhanced cell viability, attenuated ROS generation, and inhibited the opening of the mitochondrial permeability transition pore (mPTP). Furthermore, icariin mitigated DOX-induced apoptotic cell death and restored autophagic flux, as evidenced by the downregulation of beclin-1 expression and reduced LC3-II lipidation. These protective effects were accompanied by improved mitochondrial function, decreased Caveolin-1 levels, and specific suppression of PDE5a activity. Collectively, these findings underscore the therapeutic potential of icariin in alleviating DIC, primarily through its antioxidative, mitochondrial-stabilizing, and autophagy-regulating mechanisms.[101]

Eupatilin

Eupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone, available as a commercial drug, Stillen®), a phenolic flavone isolated from *Artemisia* species, exerts anti-inflammatory, anti-tumor, antioxidant, antiallergic, cardioprotective, nephroprotective and neuroprotective activities.[207] Eupatilin has been documented to exhibit significant therapeutic potential in the treatment of asthma, hyperlipidemia, hyperuricemia, renal injury, endometrial fibrosis, gastritis, periodontitis, hepatic fibrosis, pulmonary fibrosis, renal cell carcinoma and cervical cancer.[208] In the field of cardiovascular disease, eupatilin has demonstrated protective effects against DIC by modulating oxidative stress, inflammation, and apoptosis. In a murine model of DIC, daily administration of eupatilin over a 7-day period significantly improved cardiac function, attenuated oxidative stress, and suppressed inflammatory and apoptotic responses. Mechanistic studies revealed that eupatilin exerts its cardioprotective effects primarily through the activation of the PI3K-Akt signaling pathway. These findings underscore the therapeutic potential of eupatilin as a novel agent for alleviating DIC, with its protective mechanisms centered on the regulation of oxidative stress, inflammation, and apoptosis.[102]

Luteolin

Luteolin (3′,4′,5,7-tetrahydroxyflavone), a member of the flavone subgroup within flavonoids, is a plant-derived secondary metabolite existing in aglycone or glycosidic forms across traditional herbs, vegetables, and fruits.[209] Extensive

research has demonstrated that luteolin (Lut) exhibits a wide spectrum of pharmacological activities, including antioxidative, antitumor, anti-inflammatory, antidiabetic, autophagic-regulatory, antimicrobial, cardioprotective, and neuroprotective effects. These activities are mechanistically linked to its modulation of key signaling pathways such as eNOS/Keap1/Nrf2, Ampk/PKC, p38 MAPK/NF-κB, JAK/STAT, Ras/Raf/MEK/Erk, PI3K/Akt, and Wnt/β-catenin.[210] In TCM, Lut-rich plants have historically been employed to manage conditions including hypertension, inflammatory disorders, obesity, diabetes, and cancer.[209] Lut demonstrates dual therapeutic potential by ameliorating DIC while enhancing its antitumor efficacy. In vitro studies in H9c2 and AC16 cardiomyocytes revealed that Lut attenuated DOX-induced oxidative stress, mitochondrial fission, and apoptosis. Mechanistically, Lut suppressed Drp1 upregulation and Ser616 phosphorylation, thereby preserving mitochondrial integrity. In vivo validation in zebrafish and murine models confirmed that Lut preserved ventricular function and prevented cardiac damage post-DOX exposure. Notably, Lut synergistically enhanced DOX's antitumor activity in triple-negative breast cancer by inhibiting proliferation, metastasis, and promoting apoptosis, underscoring its role as both a cardioprotectant and chemotherapeutic adjuvant.[211] Further studies in a rat model demonstrated that Lut alleviates DIC via activation of the Akt/Bcl-2 signaling pathway. Treatment with Lut restored cardiac function, normalized heart weight, and reduced serum biomarkers of cardiac injury, including brain natriuretic peptide, CK-MB, cTnT, and LDH. Lut mitigated oxidative stress by decreasing MDA levels and enhancing SOD activity. At the molecular level, Lut downregulated pro-apoptotic Bax and Caspase-3 while upregulating anti-apoptotic Bcl-2, of which effects mediated through inhibition of Phlpp1 and subsequent Akt/Bcl-2 pathway activation.[103] Luteolin-7-O-glucoside (cynaroside), a glycosylated derivative predominantly found in *honeysuckle*, exhibits cardioprotective effects by targeting oxidative stress, pyroptosis, and mitochondrial dysfunction. In a murine DIC model, cynaroside improved cardiac function, reduced oxidative damage, and maintained apoptotic homeostasis. In vitro, it modulated pyroptosis-related genes (Nlrp3, Caspase-1, Gsdmd) and enhanced mitochondrial function via activation of the Ampk/Sirt3/Nrf2 axis.[104] Additionally, cynaroside mitigates DIC by regulating the Pten/Akt and Erk pathways. In H9c2 cells, cynaroside pretreatment attenuated morphological damage, increased viability, and reduced ROS generation and mitochondrial depolarization. Molecular analyses revealed that cynaroside upregulated phosphorylated Pten while downregulating p-Akt, p-Erk, p-mTOR, and p-GSK-3β, counteracting DOX-induced pro-apoptotic signaling.[105] Collectively, Lut and its derivatives exhibit multifaceted cardioprotective effects against DIC through modulation of oxidative stress, apoptosis, mitochondrial dynamics, and critical signaling pathways. These findings highlight their potential as adjuvant therapies to mitigate chemotherapy-associated cardiotoxicity while enhancing oncological efficacy.

Diosmin

Diosmin (3′,5,7-trihydroxy-4′-methoxyflavone-7-rutinoside, DS), a flavone glycoside chemically derived from the oxidation of hesperidin, is predominantly sourced from citrus fruits.[212] First isolated from *Scrophularia nodosa* L. in 1925, DS was introduced as a therapeutic agent in 1969 for managing vascular disorders such as chronic venous insufficiency, hemorrhoids, and varicose veins.[213] Extensive preclinical studies have established DS's diverse pharmacological properties, including anti-inflammatory, antioxidant, anti-tumor, antidiabetic, antihyperlipidemic, cardioprotective, neuroprotective, hepatoprotective, antimicrobial, and antifibrotic effects across various disease models.[214] Its therapeutic efficacy is largely attributed to its potent antioxidant activity, which mitigates oxidative stress-mediated cellular damage.[215] The previous study has demonstrated the cardioprotective property of DS against DIC without compromising its antitumor efficacy. In vitro studies revealed that DS preserved DOX's cytotoxic activity against MCF-7 breast cancer cells. In a female Wistar rat model, DS pretreatment significantly attenuated DOX-induced cardiac injury. DOX administration alone induced ECG abnormalities, elevated serum cardiac biomarkers (CK-MB, cTnT, and LDH), increased cardiac MDA and IL-1β levels, and reduced IL-10 and SOD activity. DOX also upregulated pro-apoptotic Bax, TNF-α, and HIF-1α, while downregulating anti-apoptotic Bcl-2 in cardiac tissues, accompanied by severe histopathological damage. In contrast, DS pretreatment normalized ECG parameters, suppressed IL-1β, enhanced IL-10 and SOD activity, and reduced MDA levels. DS also downregulated Bax, TNF-α, and HIF-1α while upregulating Bcl-2, effectively ameliorating DOX-induced histopathological alterations. These findings suggest that DS mitigates DIC through inhibition of inflammatory signaling pathways; however, the precise molecular mechanisms require further elucidation.[106]

Flavanones

Liquiritigenin

Liquiritigenin (LQG, 4′,7-dihydroxyflavanone) is a major bioactive flavanone ingredient extracted from *Glycyrrhizae Radix et Rhizoma* (Gan Cao), which is widely used in TCM.[216] Holding various pharmacological and biochemical properties, such as neuroprotective, antibacterial, antioxidative, anti-inflammatory, anti-periodontitis, anti-asthmatic, anti-diabetic, anti-osteoporosis, hepatoprotective, nephroprotective, anti-mutagenic and anti-tumor activities, LQG-enriched medicinal plants were widely employed in the treatment of depression, anxiety, Parkinson's disease, Alzheimer's disease, stroke, nociception and brain glioma.[217] While LQG is widely recognized for its neuropharmacological properties, recent studies have uncovered its cardioprotective potential against DIC. LQG was shown to ameliorate DOX-induced chronic heart failure (CHF) by targeting the Arhgap18/RhoA/Rock1 signaling axis. In both in vitro CHF cell models and in vivo rat models of DIC, LQG significantly improved cardiac function, reduced ROS accumulation, and suppressed cardiomyocyte apoptosis. Mechanistic investigations revealed that DOX treatment upregulated active RhoA expression while downregulating Arhgap18, thereby promoting ROS generation and apoptotic signaling. Overexpression of Arhgap18 attenuated these pathological effects, whereas Arhgap18 knockdown exacerbated them-a phenomenon reversible by RhoA inhibition. LQG mimicked the protective effects of Arhgap18 overexpression in CHF models and counteracted the detrimental consequences of Arhgap18 knockdown. In vivo, LQG administration enhanced left ventricular systolic pressure, reduced left ventricular end-diastolic pressure, and lowered serum levels of LDH and BNP, demonstrating its therapeutic efficacy in mitigating cardiac dysfunction.[107] Nevertheless, LQG has low aqueous solubility and lipid solubility resulting the low bioavailability in vivo.[218] To optimize its bioavailability and cardioprotective efficacy, a LQG-loaded submicron emulsion (Lq-SE) was developed using high-pressure homogenization and optimized through central composite design response surface methodology (CCD-RSM). Pharmacokinetic studies revealed a 59.5% increase in oral bioavailability compared to free LQG, highlighting the formulation's enhanced delivery potential. In a murine model of DIC, Lq-SE treatment significantly reduced serum levels of cardiac injury biomarkers and ameliorated histopathological damage in cardiac tissues. Lq-SE attenuated oxidative stress by decreasing ROS levels, enhancing antioxidant enzyme activity, and downregulating NADPH oxidase isoforms Nox4 and Nox2. Furthermore, Lq-SE modulated inflammatory responses through inhibition of the MAPK/ NF-κB signaling pathway and suppressed cardiomyocyte apoptosis. These findings position Lq-SE as a promising therapeutic strategy to mitigate DIC, potentially enabling safer and more effective chemotherapy regimens.[108]

Naringin

Naringin (5,7-trihydroxyflavonone-7-rhamnoglucoside) commonly presented as naringenin-7-O-rhamnoglucoside comes under the category of flavanone glycoside isolated from grapes and citrus fruits.[219] Naringin exhibits a broad spectrum of pharmacological and biological properties, demonstrating efficacy in modulating endogenous mediators to confer multiple physiological benefits. These include potent anti-oxidative, anti-inflammatory, and anti-apoptotic activities. The compound manifests therapeutic potential across diverse pathological conditions, notably neurodegeneration, asthma-induced tissue damage, chemical hepatotoxicity, tardive dyskinesia, and ligament regeneration. Of particular significance, preclinical investigations have consistently revealed naringin's protective effects in organ-specific injuries, particularly within intestinal, cardiac, and pulmonary systems. Mechanistically, naringin modulates key signaling pathways to suppress the production of pro-inflammatory cytokines, such as Keap1/Nrf-2, RhoA/Rock, Ppar/Stat1, PI3K/Akt, and MAPK/Ampk.[220] Naringin has demonstrated cardioprotective efficacy in both in vitro and in vivo models of DIC. Its protective mechanisms are primarily attributed to the mitigation of oxidative stress and preservation of mitochondrial function. In a rat model of DOX-induced cardiac injury, naringin significantly improved cardiac functional parameters by MDA levels, elevating GSH concentrations, and enhancing the activities of antioxidant enzymes, including SOD and CAT. Furthermore, naringin restored the impaired activities of mitochondrial electron transport chain complexes I–IV, which are critical for maintaining cellular energy homeostasis and redox balance.[109] To elucidate the molecular basis of naringin's cardioprotection, studies have focused on its interaction with the p38 MAPK signaling pathway. In H9c2 cardiomyocytes, pretreatment with naringin markedly increased cell viability and attenuated DOX-induced ROS accumulation. These effects were paralleled by the suppression of p38 MAPK phosphorylation, a key mediator of oxidative

stress and apoptosis. Notably, the protective outcomes mirrored those observed with SB203580, a selective p38 MAPK inhibitor, confirming the pathway's central role. These findings collectively establish that naringin alleviates DIC by inhibiting p38 MAPK activation, thereby reducing oxidative damage and preserving mitochondrial integrity.[110]

Hesperidin

Hesperidin (3′,5,7-trihydroxyflavanone-7-rhamnoglucoside, HES), a prominent member of the flavanone subclass within flavonoids, is predominantly found in citrus fruits of the Rutaceae family, such as oranges, grapefruits, tangerines, limes, and lemons.[221] Recognized for its broad-spectrum health-promoting effects encompassing anti-inflammatory, antioxidant, anti-aging, anti-tumor, and antibacterial properties, HES has been extensively investigated for its therapeutic potential in managing type 2 diabetes, cardiovascular diseases, cancer, neurological disorders, and radiation-induced damage.[222,223] Furthermore, it demonstrates notable benefits in modulating cutaneous functions under both physiological and pathological conditions.[223] HES exhibits significant cardioprotective activity against DIC through its antioxidative, anti-inflammatory, and anti-apoptotic properties. In a Wistar rat model, HES administration attenuated DOX-induced cardiac injury by reducing serum levels of cardiac biomarkers (cTnI, CK-Total, CK-MB, LDH, and AST) and pro-inflammatory cytokines (IFN-γ, IL-1β, and TNF-α). Concurrently, HES enhanced antioxidant defenses by elevating GPx, SOD, and CAT activities. Histopathological analysis revealed that HES alleviated DOX-induced cardiomyocyte necrosis, sarcoplasmic vacuolization, inflammatory infiltration, and tissue disorganization.[111] A complementary study in rats demonstrated that HES mitigates DIC by restoring redox homeostasis and NO balance, highlighting its dual regulatory role in oxidative stress and vascular function.[112] Despite its therapeutic promise, hesperidin's clinical utility is constrained by low aqueous solubility and limited bioavailability. To address this, hesperidin-loaded solid lipid nanoparticles (HES-SLNs) were developed, which significantly enhanced cardioprotective efficacy in a rat model of DIC. HES-SLNs improved cardiac biomarker profiles, ameliorated histopathological damage, reduced MDA levels, and upregulated CAT and SOD activities. Additionally, HES-SLNs suppressed Caspase-3 expression, underscoring their ability to attenuate oxidative stress and apoptosis more effectively than free HES.[113] Hesperetin, the aglycone metabolite of HES, similarly protects against DIC by targeting oxidative stress and mitochondrial dysfunction. In vivo studies demonstrated that hesperetin reduced MDA levels, restored GSH content, and improved cardiac functional parameters in DOX-exposed rats. In vitro analyses revealed its capacity to mitigate DNA damage, apoptosis, and ROS generation. Mechanistically, hesperetin inhibits NF-κB and p38 MAPK signaling while suppressing Caspase-3 activation, thereby preserving mitochondrial integrity.[114]

Silibinin

Silibinin (SLB), a natural flavanone, derived from the milk thistle plant (*Silybum marianum*), was illustrated for several medicinal uses such as anti-tumor, antioxidant, anti-inflammatory, hypocholesterolemic, cardioprotective, neuroprotective, hepatoprotective, antimicrobial, and antidiabetic effects.[224] Of note, this promising natural compound has been tested for its cardioprotective activities against doxorubicin DIC. In a DOX-injured human AC16 cardiomyocyte model, SLB attenuated cellular damage by restoring the activity of the IL6st/Jak2/ Stat3 signaling axis and enhancing autophagic flux. Network pharmacology and molecular docking analyses revealed strong binding affinities (≤ -7.0 kcal/mol) between SLB and key pathway components (IL6st, Jak2, and Stat3), suggesting direct molecular interactions. Experimental validation confirmed that SLB reduced mitochondrial ROS accumulation and promoted autophagy, of which effects were abolished upon IL6st, Jak2, or Stat3 knockdown or pharmacological inhibition of autophagy (via 3-methyladenine [3-MA] or beclin1 silencing). These findings indicate that SLB exerts its cardioprotection through dual modulation of the IL6st/Jak2/ Stat3 pathway and autophagy restoration, offering a novel mechanistic strategy to counteract DIC.[115] Despite its therapeutic promise, SLB's clinical translation is hindered by poor aqueous solubility and limited oral bioavailability. To address these limitations, a silibinin-phosphatidylcholine (SLB-PC) complex was developed to enhance solubility and pharmacokinetic profiles.[225] While this formulation shows potential for improving drug delivery, its efficacy in mitigating DIC remains unexplored, warranting further preclinical and clinical investigation.

Naringenin

Naringenin (4′,5,7-trihydroxyflavanone, NAR), a flavanone compound and the aglycone of naringin, is abundant in tomatoes, citrus fruits, and grapefruits.[226] Despite its limited water solubility and subsequent bioavailability challenges,[227] NAR exhibits diverse pharmacological effects, including antidiabetic, anti-tumor, antimicrobial, antiobesity, gastroprotective, immunomodulatory, cardioprotective, nephroprotective, and neuroprotective activities, primarily attributed to its antioxidative and anti-inflammatory properties.[228] In a Dalton's lymphoma ascites (DLA) tumor-bearing mouse model, NAR demonstrated dual functionality by alleviating DOX-induced systemic toxicity while enhancing chemotherapeutic efficacy. DOX treatment induced marked disruptions in hematological parameters, antioxidant enzyme levels (eg, SOD, CAT), and increased lipid peroxidation (MDA) across multiple organs, including the heart, kidney, liver, spleen, and tumor tissues. NAR supplementation restored tissue integrity, reduced oxidative damage, diminished tumor burden, and alleviated hypoxia within the tumor microenvironment, highlighting its potential to improve therapeutic outcomes while minimizing off-target toxicity.[116] Additionally, in a rat model of DIC, NAR significantly improved cardiac function by restoring SOD, GPx, and CAT activities while reducing MDA levels. NAR attenuated the DOX-induced upregulation of inflammatory mediators, including TGF-β1, TNF-α, IL-6, and IL-10, and ameliorated histopathological damage such as myocardial necrosis and inflammatory infiltration.[117] Moreover, NAR pretreatment in rats normalized DOX-induced alterations in serum LDH and CPK levels, reduced lipid peroxidation, and restored cardiac antioxidant enzyme activities (SOD, GST, CAT). Furthermore, NAR reversed DOX-mediated depletion of reduced GSH and total NO content in cardiac tissues, suggesting its role in balancing redox homeostasis and vascular function.[118] Similar to NAR, Naringenin-7-O-glucoside (NARG), is a glycosylated derivative isolated from *Dracocephalum rupestre* Hance,[119] which is capable of protecting against DIC by enhancing endogenous antioxidant defense and preventing apoptosis. In H9c2 cardiomyocytes, NARG pretreatment upregulated expression of Nqo1, Gclm and Gclc, key components of the cellular antioxidant system. Mechanistically, NARG promoted phosphorylation of Erk1/2, facilitating Nrf2 nuclear translocation to activate antioxidant gene expression.[120] Furthermore, NARG was demonstrated to exert cardioprotective role by stabilizing membrane integrity and calcium signaling. In DOX-treated H9c2 cells, NARG alleviated morphological damage, enhanced viability, reduced LDH and CK leakage, and suppressed intracellular ROS and Ca²□ overload. These effects were associated with increased GPx activity, though the precise molecular mechanisms remain to be elucidated.[19]

7-Hydroxyflavanone

7-Hydroxyflavanone (7H), a member of the flavanone class, is a naturally occurring compound isolated from plants such as *Flourensia oolepis, Virola surinamensis, Zuccagnia punctata*, and *Empetrum nigrum* (black crowberry).[229] It exhibits diverse pharmacological properties, including anti-tumor, anthelmintic, antioxidative, and antifungal activities, as well as inhibitory effects on the 20S proteasome and aromatase enzymes.[121] Despite its broad bioactivity, no studies to date have explored its relevance to CVDs beyond DIC. A pioneering study revealed that 7H conferred protection against DIC by targeting oxidative stress and apoptosis. In an in vitro model using H9c2 cardiomyocytes exposed to DOX, 7H co-treatment significantly attenuated cardiac damage by enhancing total GSH content and SOD activity, while reducing ROS accumulation, MDA production, IL-6 secretion, and Caspase-3/7 activity. Furthermore, 7H restored mitochondrial bioenergetics, preserved mitochondrial membrane potential, and upregulated the expression of Pgc-1α, a master regulator of mitochondrial biogenesis. These effects were mechanistically linked to the activation of Ampk, a critical sensor of cellular energy status.[121] These findings suggest that 7H may serve as a promising therapeutic candidate for mitigating DIC through its dual antioxidative and mitochondrial protective mechanisms. Future studies should investigate its broader applicability in CVDs and validate its efficacy in preclinical models to advance translational potential.

Chalcone

Licochalcone A

Licochalcone A (Lico A), a bioactive chalcone derivative (3-dimethylallyl-4,4′-dihydroxy-6-methoxychalcone), is isolated from the roots of *Glycyrrhiza* species (licorice), a cornerstone herb in TCM with historical applications in treating microbial infections, inflammatory disorders, and cancer.[230,231] As a principal constituent of licorice, Lico A exhibits a broad pharmacological spectrum, including anti-tumor, anti-inflammatory, antioxidant, antimicrobial, antidiabetic,

neuroprotective, and cardioprotective activities. These effects are mediated through modulation of critical signaling pathways such as PI3K/Akt/mTOR, p53, NF-κB, and p38 MAPK, alongside interactions with targets including TNF-α, VEGF, Fas/FasL, and Caspases.[232] Lico A demonstrates protective efficacy against DIC by targeting oxidative stress and ferroptosis. In a murine DIC model, Lico A administration improved serum cardiac biomarkers, restored myocardial histoarchitecture, and normalized electrocardiographic abnormalities. In vitro, Lico A enhanced viability in DOX-injured H9c2 cardiomyocytes, reduced ROS, MDA, and ferrous iron levels, and elevated the GSH/glutathione disulfide (GSSG) ratio, indicative of restored redox homeostasis. Mechanistically, Lico A activated the PI3K/Akt/Mdm2 axis, suppressing p53 accumulation while upregulating ferroptosis-related proteins Slc7a11 and Gpx4. Crucially, PI3K/Akt pathway inhibition or p53 overexpression abolished these protective effects, confirming the pathway's centrality.[122] Complementary studies employing network pharmacology and ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS/MS) identified Lico A as a key licorice component mitigating DIC. In DOX-treated H9c2 cells, Lico A increased cell viability, SOD activity, and mitochondrial membrane potential while reducing MDA and ROS levels, further validating its antioxidative and mitochondrial protective roles.[123]

Aspalathin

Aspalathin (ASP), a dihydrochalcone C-glucoside exclusive to Aspalathus linearis (commonly known as rooibos), is a polyphenolic chalcone compound with well-documented biological activities, including antioxidant, anti-inflammatory, hypoglycemic, mitochondrial protective, and anti-apoptotic properties.[233] Notably, ASP exhibits therapeutic potential for metabolic syndrome management, particularly type 2 diabetes (T2D) and its complications, through modulation of glucose/lipid metabolism and activation of critical signaling pathways such as p53, PI3K/Akt, Ampk, and mTOR.[234] While substantial evidence supports its protective effects against hyperglycemia-induced oxidative damage, ischemia/reperfusion injury, and cardiac lipid toxicity,[235–237] research on ASP's cardioprotective efficacy against DIC remains limited. Recent studies, however, highlight ASP's ability to mitigate DIC via dual regulation of oxidative stress and apoptosis. In H9c2 cardiomyoblasts, ASP counteracted DOX-induced oxidative damage by upregulating antioxidant enzymes (SOD, CAT, GSH) while suppressing ROS accumulation, lipid peroxidation (MDA), and apoptotic signaling.[124] Mechanistically, ASP exerts cytoprotection in a p53-dependent manner by enhancing the Bcl-2/Bax ratio and attenuating apoptosis. Intriguingly, this effect coincides with Ampk/Foxo1-mediated activation of autophagy-related genes (Atgs) and subsequent p62 degradation, suggesting a synergistic interplay between apoptosis inhibition and autophagy induction.[125] Importantly, co-administration of ASP with DOX preserved the latter's antitumor efficacy in Caov-3 ovarian cancer cells, underscoring its clinical translatability.[125] Taken together, these findings provide a credible evidence by which ASP co-treatment could protect against DIC without comprising its chemotherapeutic outcomes.

Cardamonin

Structurally identified as a 2′,4′-dihydroxy-6′-methoxychalcone, cardamonin (CAR), a member of the chalcone family, is a natural organic compound predominantly found in high concentrations within the seeds of *Alpinia katsumadai*.[238] CAR exhibits a broad spectrum of pharmacological effects, such as antinociceptive, anti-inflammatory, antioxidant, cytotoxic, antiprotozoal, antiulcer, antihistaminic, and antitumor activities. Notably, CAR has shown protective efficacy against cisplatin-induced nephrotoxicity and has been implicated in modulating redox-sensitive pathways, including the inhibition of NF-κB and Wnt activation and cytokine production.[126,238] Furthermore, due to its antioxidant, anti-inflammatory, and neuroprotective properties, CAR has been reported to mitigate the detrimental effects of oxidative stress and neuroinflammation, highlighting its potential therapeutic significance.[238] Consistently, the cardioprotective effects of CAR against DIC has been revealed by a recent study. Through both in vitro and in vivo models, CAR has been demonstrated to effectively attenuate oxidative stress, apoptosis, and inflammatory responses, which are key pathological features of DOX-induced cardiomyopathy. In DOX-treated mouse cardiomyocytes, CAR was shown to significantly activate the Nrf2 signaling pathway while inhibiting its degradation, thereby bolstering the cellular antioxidant defense system. This activation led to the upregulation of critical antioxidant enzymes, including Hmox1, Nqo1, Gclm, SOD, GSH, and CAT. Concurrently, CAR suppressed the generation of ROS and MDA, both of which are established biomarkers of oxidative stress. Additionally, CAR was found to inhibit DOX-induced cardiomyocyte apoptosis by

modulating the Caspase-3 pathway and to attenuate inflammatory responses through the downregulation of NF-κB signaling. In a murine model of DOX-induced cardiomyopathy, CAR administration significantly improved cardiac function by mitigating oxidative damage, apoptosis, and inflammation, of which effects were mechanistically linked to its potent activation of the Nrf2 signaling pathway. These findings underscore the therapeutic potential of CAR in addressing DIC.[127]

Flavonols

Galangin

Galangin (3,5,7-trihydroxyflavone, Gal), a bioactive flavonol derived from *Alpinia officinarum Hance* (Zingiberaceae),[239] exhibits a broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, anti-tumor, antimicrobial, hepatoprotective, cardioprotective, neuroprotective, and metabolic regulatory activities.[240–242] Preclinical studies demonstrate its therapeutic efficacy in diverse pathological conditions such as neurodegenerative disorders, cardiovascular/cerebrovascular diseases, diabetes, hepatic injury, asthma, and inflammatory arthritis.[240–242] Mechanistically, Gal modulates key signaling pathways including p38 MAPK, NF-κB, PI3K/Akt, Sirt1, Trpv1, Nrf2, and Nlrp3 to counteract oxidative stress, inflammation, and cellular apoptosis.[243] Emerging evidence highlights Gal's potential in mitigating doxorubicin DIC through dual targeting of oxidative stress and ferroptosis. In murine models, Gal co-administration ameliorated DOX-induced cardiac dysfunction, attenuated myocardial histopathological damage, and normalized biomarkers of oxidative injury, including reduced ROS, MDA, and NADPH oxidase activity, while restoring SOD levels.[128] Concurrently, Gal suppressed pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and activated the Nrf2/HO-1 axis, as evidenced by enhanced nuclear translocation of Nrf2 and upregulated Hmox1 expression. The critical role of Nrf2 was confirmed via ML385 (Nrf2 inhibitor), which abolished Gal's cardioprotective effects.[128] Furthermore, Gal mitigates ferroptosis, a lipid peroxidation-driven cell death, by rescuing Gpx4, Slc7a11, and FPN expression in H9c2 cardiomyocytes, while reducing iron accumulation and Ptgs2 levels.[129] Mechanistic studies reveal that Gal upregulates Gstp1, facilitating its interaction with JNK to inhibit the JNK/c-Jun pathway, thereby attenuating ferroptotic cell death.[129] Galangin represents a promising natural cardioprotectant against DIC, synergistically targeting oxidative stress, inflammation, and ferroptosis via Nrf2/Hmox1 and Gstp1/JNK pathways.

Morin

Morin (3,5,7,2′,4′-pentahydroxyflavone) is a natural flavonol predominantly extracted from the fruits, stems, and leaves of plants belonging to the *Moraceae* family, has been extensively studied for its therapeutic potential.[244] Specifically, it demonstrates free radical scavenging, antioxidant, anti-inflammatory, anti-tumor, antimicrobial, antidiabetic, anti-arthritis, cardioprotective, neuroprotective, nephroprotective, and hepatoprotective properties. These multifaceted pharmacological activities are mediated through the modulation of key cellular signaling pathways, including NF-κB, MAPK, JAKs/STATs, Keap1/Nrf2, ER stress, mitochondrial-mediated apoptosis, Wnt/β-catenin, and the mTOR pathways. Accordingly, accumulating evidence indicates that morin exhibits a wide range of beneficial effects against numerous chronic and degenerative diseases.[245] Recently, morin has been demonstrated to exert protective effects against DIC and neurotoxicity by attenuating oxidative stress, inflammation, and apoptosis. In a rat model, morin administration significantly improved cardiac function, as evidenced by reduced serum levels of cardiac biomarkers, including LDH, CK-MB, and cTnI, alongside amelioration of histopathological damage in cardiac tissues. Morin enhanced the endogenous antioxidant defense system by elevating GSH levels and increasing the activities of key antioxidant enzymes, such as SOD, CAT, and GPx, while concurrently reducing MDA levels, a marker of lipid peroxidation. Furthermore, morin suppressed DOX-induced inflammatory responses in both cardiac and brain tissues by downregulating the expression of pro-inflammatory mediators, including TNF-α, IL-1β, and NF-κB. The compound also exhibited anti-apoptotic effects by upregulating the expression of Bcl-2 and inhibiting Caspase-3 activation. In brain tissues, morin improved neural signaling through the modulation of AChE activity and reduced the levels of glial fibrillary acidic protein (GFAP), indicative of its neuroprotective potential. Collectively, these findings underscore morin's dual cardioprotective and neuroprotective properties against DOX-induced toxicity, mediated via its antioxidant, anti-inflammatory, and anti-apoptotic mechanisms.[130]

Myricitrin

Myricitrin (myricetin-3-O-α-rhamnoside), a naturally occurring flavonol glycoside predominantly isolated from *Myrica rubra* and other dietary plants, has attracted substantial scientific interest due to its multifaceted pharmacological properties.[246] Beyond its established application as a flavor modifier in food and beverages, this compound exhibits a remarkable spectrum of bioactivities encompassing antioxidant, anti-inflammatory, antinociceptive, anti-atherosclerotic, hepatoprotective, and anti-fibrotic effects.[247] Emerging evidence from both in vitro and in vivo studies particularly highlights its therapeutic potential in cardiovascular pathologies through multimodal mechanisms. Experimental models have elucidated myricitrin's cardioprotective efficacy against DOX-induced myocardial injury. In DOX-challenged rats, myricitrin administration significantly attenuated myocardial damage, as quantified by improved LVEF, reduced serum CK-MB, and histopathological amelioration of myocardial architecture. At the cellular level, myricitrin demonstrated cytoprotection against DOX-induced cardiomyocyte apoptosis through dual modulation of oxidative homeostasis and apoptotic signaling. These effects were associated with enhanced SOD activities, stabilized MMP, and regulation of apoptosis-related markers. Mechanistic studies reveal its regulation of stress-responsive pathways, particularly through inhibition of the Erk/p53 signaling cascade, thereby preventing mitochondrial dysfunction-mediated apoptosis.[131] Given its recognized safety profile by international regulatory bodies and demonstrated efficacy across experimental models, myricitrin presents as a promising phytochemical candidate for developing nutraceutical interventions targeting oxidative stress-associated pathologies.

Quercetin

Quercetin (3,5,7,3′,4′-pentahydroxyflavone), a prominent phytochemical within the flavonol subclass of flavonoid polyphenols, is ubiquitously distributed in fruits, vegetables, beverages, flowers, leaves, and seeds, with onions representing its richest dietary source.[248] As a multifunctional flavonoid, quercetin exhibits a broad spectrum of pharmacological properties, including antihypertensive, antihyperlipidemic, antihyperglycemic, antioxidant, antiviral, anti-tumor, anti-inflammatory, antimicrobial, neuroprotective, and cardioprotective effects.[249] Extensive in vivo and in vitro studies have elucidated its therapeutic potential in addressing neurodegeneration, diabetes, cancer, and inflammation, solidifying its current utilization in diverse pharmaceutical formulations.[250] Of particular significance is quercetin's protective role against DIC, mediated through precise modulation of molecular and signaling pathways. Mechanistically, quercetin attenuates oxidative stress by upregulating critical antioxidant enzymes such as SOD, CAT, and GPx, while significantly reducing ROS and lipid peroxidation markers like MDA.[132,133] Concurrently, it enhances mitochondrial function by restoring MMP, improving the GSH/GSSG ratio, and elevating expression of mitochondrial protective proteins, including Bmi-1 and 14-3-3γ.[132,134] In apoptotic regulation, quercetin suppresses pro-apoptotic factors such as p53, Bid, and Nox1, while upregulating anti-apoptotic Bcl-2 and modulating Caspase-3 activation to mitigate myocardial apoptosis.[135] It further orchestrates cellular energy homeostasis via activation of the Ampk pathway, enhancing downstream effectors Pparα and Pgc-1α, thereby promoting energy metabolism and reducing oxidative myocardial injury.[136] The Akt kinase pathway, integral to anti-apoptotic signaling and ischemic tolerance, is also activated by quercetin.[137] Quercetin's anti-inflammatory action is achieved through inhibition of pro-inflammatory mediators, including TNF-α and iNOS, coupled with reduction of NO production.[138] In DIC models, it attenuates oxidative damage and apoptosis by suppressing the SOD/p53 signaling axis.[139] Synergistic strategies reveal that quercetin enhances the cardioprotective efficacy of agents such as losartan and resveratrol through cooperative pathway modulation, without compromising DOX's anti-tumor activity.[140,141] Advanced delivery systems, including liposomal formulations and polymeric micelles, have been engineered to improve its bioavailability and therapeutic precision via sustained release and targeted delivery.[251] Collectively, these molecular insights underscore quercetin's capacity to counteract the multifactorial mechanisms underlying chemotherapy-induced cardiotoxicity, positioning it as a promising adjuvant in clinical oncology. Further research is warranted to optimize its pharmacokinetic profile and validate its translational potential in combinatorial cancer therapies.

Fisetin

Fisetin (3,3′,4′,7-tetrahydroxyflavone), a flavonol subgroup member within the flavonoid class, occurs naturally in fruits and vegetables including apples, persimmons, grapes, cucumbers, and onions at concentrations ranging from 0.1 to 160 μg/g.[252] Strawberries represent the richest dietary source.[253] Fisetin demonstrates pleiotropic pharmacological activities with therapeutic potential across multiple disease domains, such as anti-tumor (PI3K/Akt/mTOR and Wnt/β-catenin, Trail and VEGF signal), anti-inflammatory (NF-κB and NO signal in hepatic ischemia/reperfusion), antioxidant (Nrf2 signal), neuroprotective, osteoprotective activity (Pten and mTORC2 signal).[254] Of particular pharmacological significance, fisetin has been demonstrated to attenuate DIC through coordinated modulation of oxidative stress, inflammatory responses, and apoptotic pathways. In H9c2 cardiomyoblasts, fisetin was shown to reduce DOX-induced cell death in a dose-dependent manner, primarily through inhibition of the IGF-II receptor (IGF-IIR)-dependent apoptotic pathway via estrogen receptor (ER)-α/-β activation. In vivo studies using rat models revealed that fisetin administration improved cardiac functional parameters, decreased serum levels of cardiac injury markers (CK-MB, LDH, AST, ALT, ALP), and enhanced antioxidant defense mechanisms through elevated SOD activity and GSH levels, accompanied by reduced MDA and NO concentrations.[142] Mechanistic investigations further demonstrated fisetin-mediated suppression of pro-inflammatory mediators (COX-II, TNF-α, IL-1β) and apoptotic markers (Caspase-3, cTn-I, iNOS), with these effects observed at both transcriptional and translational levels. Histopathological evaluations provided structural confirmation of these protective effects, demonstrating reduced myocardial tissue damage and oxidative injury markers in fisetin-treated specimens.[143] These findings highlight fisetin's ability to modulate key molecular pathways involved in oxidative stress, inflammation, and apoptosis, providing a promising therapeutic approach to mitigate DIC in cancer treatment.

Rutin

Rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside), a flavonol glycoside ubiquitously present in crops such as apples, buckwheat, tea, and passion flower, is also known as rutoside, quercetin-3-O-rutinoside, or sophorin.[255] The compound derives its name from *Ruta graveolens L*., a primary natural source.[256] Recognized for its diverse biological activities including anti-inflammatory, antioxidant, anti-tumor, antimicrobial, antihyperglycemic, neuroprotective, nephroprotective, cardioprotective, and hepatoprotective effects, rutin has garnered significant interest as a therapeutic agent for managing cancer, neurodegenerative disorders, cardiovascular diseases, and diabetes.[257,258] Of particular note are rutin's cardioprotective properties against anthracycline-induced cardiotoxicity, such as that caused by DOX and pirarubicin (THP). Mechanistic studies reveal that rutin attenuates cardiomyocyte apoptosis and autophagy through Akt signaling pathway, leading to improved cardiac function and reduced myocardial damage in DOX-treated murine models.[144] In THP-induced cardiotoxicity, rutin mitigated oxidative stress and apoptosis by upregulating miR-22-5p expression and downregulating Rap1/Erk pathway components, thereby.[145] Furthermore, rutin suppresses miR-125b-1-3p expression, enhancing JunD signaling to reduce ROS accumulation and apoptotic activity.[146] Rutin also activates PI3K/Akt/ mTOR pathway, bolstering antioxidative defenses and angiogenesis, which collectively enhance cell survival and cardiac function in THP-treated models.[147] These findings underscore rutin's ability to concurrently regulate oxidative stress, apoptosis, autophagy, and angiogenic pathways, offering a multifaceted therapeutic strategy to counteract DIC while preserving cardiac integrity.

Kaempferol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one), a naturally occurring flavonol glycoside, is widely distributed in fruits and vegetables such as onions, broccoli, strawberries, and grapes, as well as in medicinal plants like *Ginkgo biloba*.[259] This compound and its glycosylated derivatives exhibit a broad spectrum of pharmacological activities, including cardioprotective, neuroprotective, anti-inflammatory, antidiabetic, antioxidant, antimicrobial, and antitumor effects.[259,260] In CVD, kaempferol's anti-inflammatory activity is mediated through suppression of pro-inflammatory cytokines (eg, IL-1β, TNF-α) and downregulation of adhesion molecules such as Vcam1, Icam1, and Mcp1, thereby attenuating monocyte infiltration.[261] Its antioxidant properties involve activation of Nrf-2 pathway and upregulation of eNOS/dimethylarginine dimethylaminohydrolase II (DDAH II) expression, effectively reducing ROS accumulation.[262] Preclinical studies in animal models demonstrate kaempferol's ability to ameliorate high-fat diet-

induced vascular dysfunction, dyslipidemia, and oxidative stress, while concurrently inhibiting inflammation and apoptosis via modulation of the GPER/PI3K/Akt signaling axis.[263] In vitro investigations further reveal its endothelial protective effects, including reduced apoptosis in HUVECs, and inhibition of macrophage differentiation. Central to its molecular mechanisms are suppression of NF-κB and MAPK inflammatory pathways, activation of the Nrf-2-mediated antioxidant response, and regulation of vascular tone-related signaling.[264] Kaempferol exhibits significant cardioprotective effects against DIC through dual modulation of p53-mediated apoptotic signaling and Erk pathway.[148] In a rat model, prophylactic kaempferol administration attenuated DOX-induced oxidative stress, mitochondrial dysfunction, and cardiomyocyte apoptosis. DOX treatment impaired cardiac growth and disrupted Bcl-2 expression, which were counteracted by kaempferol through suppression of p53 expression and inhibition of its binding to the Bax promoter, thereby blunting mitochondrial apoptosis. Complementary in vitro studies corroborated these findings, demonstrating kaempferol's inhibition of mitochondrion-dependent apoptotic pathways. Notably, kaempferol selectively inhibited Erk 1/2 phosphorylation without affecting p38 or JNK pathways, underscoring its specificity in modulating stress-responsive signaling. These dual mechanisms that attenuation of mitochondrial apoptosis and selective Erk pathway regulation highlight kaempferol's potential as an adjunctive therapy to mitigate DOX-induced cardiac damage while preserving chemotherapeutic efficacy.

Robinin

Robinin (kaempferol-3-O-robinoside-7-O-rhamnoside), a naturally occurring flavonol glycoside, was initially isolated from the aerial parts of *Astragalus falcatus* Lam.[265] This bioflavonoid has been demonstrated to exhibit multifunctional pharmacological activities, including anti-inflammatory, anti-osteoarthritis, anti-tumor, neuroprotective, nephroprotective, cardioprotective, and antioxidant effects, primarily through modulation of critical signaling pathways such as TLR2/PI3K/Akt, TLR/NF-κB, and Hmgb1/Rage signaling.[266] Notably, experimental evidence from Sprague Dawley rat model indicated that robinin attenuated DIC via regulation of the TGF-β1 signaling pathway.[149] In this study, DOX administration induced significant elevations in cardiac injury biomarkers (LDH and CPK) and hepatic toxicity markers (serum glutamate oxaloacetate transaminase [SGOT] and serum glutamate pyruvate transaminase [SGPT]). Concurrently, DOX treatment increased lipid peroxidation levels and pro-inflammatory mediators (Cox2, Lox15), while markedly suppressing antioxidant enzyme activities. Molecular analyses revealed DOX-induced dysregulation of TGF-β1 signaling components, including altered expression of Smad2, Smad3, Mdm2, Smad7, Cdkn2a, and Smad4. Apoptotic protein expression profiles were similarly affected, with increased p53 and Bax levels accompanied by decreased Bcl-2 expression. Co-administration of robinin effectively normalized these pathological alterations, restoring antioxidant capacity and attenuating oxidative stress. Complementary in vitro investigations demonstrated that robinin pretreatment significantly reduced apoptotic rates through enhancement of endogenous antioxidant activity with concomitant reduction in MDA and LDH levels and inhibition of ROS generation. Notably, comparative analyses with the clinical cardioprotectant dexrazoxane (DEX) revealed differential efficacy profiles, while DEX showed superior protection against DIC, robinin exhibited significant protective effects against both H_2O_2 and DOX induced stress.[150] These findings collectively highlight robinin's potential as a multifactorial therapeutic agent for mitigating chemotherapy-associated cardiac damage.

Isorhamnetin

Isorhamnetin (3-methylquercetin), a naturally occurring flavonol chemically defined as 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one, is predominantly isolated from *Hippophae rhamnoides* L. (sea buckthorn) fruits and *Ginkgo biloba* L. leaves.[267] Accumulating preclinical evidence underscores its therapeutic potential in various disease, attributed to its multifaceted pharmacological properties, including anti-atherosclerotic, lipid-lowering, anti-inflammatory, antioxidant, antithrombotic, antiplatelet, antihypertensive, and cardioprotective effects.[268] Mechanistically, isorhamnetin modulates critical signaling pathways such as PI3K/Akt/Pkb, NF-κB, and MAPK cascades, thereby regulating downstream inflammatory cytokines and cellular kinases.[269] In the context of DIC, isorhamnetin demonstrates robust cardioprotection through dual modulation of oxidative stress and apoptotic pathways.[151] In vivo studies in rat models revealed that isorhamnetin pretreatment significantly attenuated DOX-induced myocardial injury, evidenced by improved cardiac functional parameters, reduced serum levels of cardiac enzymes (eg, CK-MB, LDH), and alleviated

histopathological alterations such as myocardial vacuolation. Complementary in vitro experiments using H9c2 cardiomyocytes further confirmed its protective role, showing that isorhamnetin reduced intracellular ROS accumulation and suppressed mitochondrial apoptosis via inhibition of Caspase activation. Additionally, isorhamnetin attenuated DOX-triggered MAPK pathway activation, further mitigating cardiomyocyte damage. Notably, isorhamnetin exhibits dual therapeutic efficacy while protecting cardiac tissue from DOX toxicity, it synergistically enhances DOX's anti-tumor activity in MCF-7, HepG2, and Hep2 cancer cell lines. This dual action highlights its potential as an adjunctive therapy to mitigate chemotherapy-induced cardiotoxicity without compromising antitumor efficacy.

Anthocyanins

Anthocyanins, a subclass of flavonoids widely distributed as natural pigments in fruits and vegetables, exist predominantly in their glycosylated forms, which are chemically derived from their aglycone counterparts, anthocyanidins.[270] Among identified anthocyanidins, six are most prevalent: cyanidin (Cy), delphinidin (Dp), malvidin (Mv), pelargonidin (Pg), peonidin (Pn), and petunidin (Pt).[271] These compounds have garnered significant scientific interest due to their high dietary bioavailability and diverse health-promoting properties, including antineoplastic, radioprotective, vasoprotective, anti-inflammatory, and chemoprotective effects, largely attributed to their potent antioxidant capacity in mitigating lipid peroxidation and LDL oxidation.[152] Of note, cyanidin-3-glucoside (C3G), a prominent anthocyanin in purple corn, demonstrates cardioprotective efficacy against DIC. In vitro studies using murine HL-1 cardiomyocytes revealed that pretreatment with purified C3G or purple corn extract significantly enhanced cell viability under DOX exposure, without compromising DOX's cytotoxic effects on human cancer cell lines. Corroborating these findings, in vivo experiments showed that mice fed a C3G-enriched diet exhibited improved survival rates and reduced histopathological cardiac damage following DOX administration, underscoring its selective cardioprotection without interfering with DOX's antitumor activity.[153] Cyanidin chloride (CyCl), identified via a deep-learning-assisted zebrafish phenotypic screening platform combined with cardiac functional analysis, emerged as a potent inhibitor of DIC. Subsequent validation in vitro and in vivo DIC models demonstrated that CyCl attenuates cardiomyocyte death, restores cardiac function, and mitigates lipid peroxidation and mitochondrial dysfunction by suppressing ferroptosis and apoptosis. Mechanistic investigations revealed that CyCl directly binds to Keap1, disrupting its interaction with Nrf2, thereby promoting Nrf2 nuclear translocation and upregulating antioxidant defenses, including Gpx4. A Keap1 R415A mutation abolished CyCl's protective effects, confirming the critical role of Keap1-Nrf2 axis modulation.[154] These findings highlight anthocyanins' dual role in cardioprotection and chemotherapeutic synergy, offering a strategic avenue to enhance the safety profile of DOX-based regimens. Further research is warranted to translate these preclinical insights into clinical applications, optimizing bioavailability and therapeutic efficacy.

Flavanols

Flavanols, a prominent class of plant-derived polyphenolic compounds, are recognized for their diverse health-promoting properties, including antioxidant, cardioprotective, anti-microbial, anti-viral, and neuroprotective, anti-inflammatory, and chemopreventive activities.[272] Structurally classified into flavan-3-ols, flavan-4-ols, isoflavan-4-ols, and flavan-3,4-ols, these metabolites have garnered significant pharmacological interest.[273] Among them, catechins, a subclass of flavan-3-ols abundant in *Camellia sinensis* (green tea), are particularly notable for their therapeutic potential.[274] Key catechin derivatives include (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC), (-)-epicatechin (EC), and (+)-catechin (CAT), all of which exhibit robust antioxidant and cytoprotective effects.[275] Catechins demonstrate significant cardioprotection against DIC via modulation of oxidative stress and apoptotic pathways. In a rat model of DIC, CAT pretreatment markedly improved cardiac function by reducing intracellular ROS levels and enhancing the activity of antioxidant enzymes, including CAT, SOD, and GST. Additionally, CAT attenuated DOX-induced apoptosis by downregulating pro-apoptotic markers (eg, Bax, Caspase-3) and restoring reduced GSH homeostasis in cardiac tissues. Histopathological assessments revealed that CAT mitigated DOX-induced myofibrillar loss, hemorrhage, and vascular congestion, while ultrastructural analysis confirmed its protective effects against mitochondrial degeneration and preservation of intercalated disc integrity.[155] Mechanistically, CAT suppressed the expression of pro-inflammatory mediators such as NF-κB, TNF-α, and iNOS, highlighting its anti-inflammatory role in cardioprotection.[156]

EGCG, the most abundant and bioactive catechin in green tea, exerts multifaceted protection against DIC. In vivo studies demonstrated that EGCG administration alleviated cardiac injury by reducing LDH release, attenuating apoptosis, and restoring mitochondrial membrane potential (ΔΨm) via upregulation of MnSOD. EGCG also ameliorated myocardial ROS generation and calcium overload, key contributors to DOX-induced cardiomyocyte dysfunction.[157] Functional assessments in isolated cardiomyocytes revealed that EGCG restored impaired contraction-relaxation dynamics, including cell shortening and the maximum velocity of contraction (+dL/dt), by enhancing both electrically- and caffeine-induced Ca^{2+} transients.[158] This suggests EGCG's ability to replenish sarcoplasmic reticulum Ca^{2+} stores, thereby improving calcium handling. Further mechanistic studies in murine models and cardiomyocytes showed that EGCG mitigated DOX-induced ECG abnormalities, leakage of cardiac enzymes (CK-MB and LDH), lipid peroxidation, and histopathological damage.[159,160] These effects were linked to the restoration of ErbB2 and Hsp70 expression, alongside suppression of NF-κB, p53, calpain-2, and Caspases-3/12.[160] Notably, co-administration of EGCG with DOX synergistically enhanced tumor growth inhibition and apoptosis induction in cancer cells, without compromising DOX's chemotherapeutic efficacy.[157] The dual cardioprotective and chemosensitizing properties of catechins, particularly EGCG, underscore their potential as adjunctive therapies in DOX-based chemotherapy. By targeting oxidative stress, calcium dysregulation, and apoptotic/inflammatory pathways, these compounds offer a strategic approach to mitigate cardiotoxicity while preserving anti-tumor activity. Future research should prioritize clinical validation of these preclinical findings, focusing on bioavailability optimization and dose-response studies to facilitate translational applications.

Flavonoids From Basic Research to Clinical Trial

Although a plenty of flavonoids have been extensively investigated for the potential application in DIC, the therapeutic value of most flavonoids is not tested by clinical trials except for 7-Monohydroxyethylrutoside and silymarin. The primary findings from basic research to clinical trial regarding 7-Monohydroxyethylrutoside and silymarin are summarized in Table 2.

7-Monohydroxyethylrutoside

7-Monohydroxyethylrutoside (monoHER), a semisynthetic flavonoid derived from hydroxyethylrutosides, has emerged as a promising cardioprotective agent against doxorubicin DIC. MonoHER's antioxidant properties have been extensively studied across various preclinical models to mitigate these deleterious effects while preserving DOX's anti-tumor efficacy. MonoHER has demonstrated high tissue uptake and stability under specific conditions, with bioavailability varying across administration routes. Intravenous and intraperitoneal injections yielded significant plasma and heart tissue concentrations, while oral bioavailability was negligible.[276,294] Pharmacokinetic studies confirmed that monoHER's protective effects are not mediated by interactions with DOX metabolism but rather by its antioxidant activity.[295] MonoHER exhibited a peak plasma concentration of approximately 130 μM (IP) and 230 μM (subcutaneous), with sustained cardioprotective levels in preclinical studies.[276] MonoHER's cardioprotective effects are primarily attributed to its antioxidant capacity, neutralizing ROS and attenuating oxidative stress pathways. Studies on neonatal rat cardiac myocytes (NeRCaMs) revealed that monoHER significantly reduced DOX-induced cytotoxicity, apoptosis, and lipid peroxidation.[277–279] MonoHER suppressed Caspase-dependent and independent apoptotic pathways, particularly by inhibiting mitochondrial damage and p53 activation. These effects were consistent across other cell types, including endothelial and ovarian cancer cells, indicating monoHER's selective cytoprotection in non-cancerous tissues.[277–279] MonoHER was compared with clinically established cardioprotective agents like dexrazoxane (ICRF-187). Preclinical studies in mice demonstrated that monoHER provided comparable or superior protection against DIC, as evidenced by reduced ECG changes (eg, ST interval prolongation), cardiomyocyte damage, and histological markers of cardiac injury.[280] Importantly, monoHER did not compromise DOX's antitumor efficacy, distinguishing it from some alternative agents. Optimal dosing schedules were critical for monoHER's efficacy. A single dose administered one hour prior to DOX injection was sufficient to confer protection, aligning with its pharmacokinetic profile.[281] Frequent dosing regimens, however, raised concerns about potential pro-oxidant effects, especially over extended periods. Long-term studies revealed that monoHER's initial cardioprotective effects diminished when dosing frequency increased,

Table 2 Flavonoids from Basic Research to Clinical Trial

Compound	Study Design	Marker	Signal	Mechanism	Ref.
7-Monohydroxyethylrutoside (monoHER)	In vivo(mice)	Bioavailability: i.v>i.p>s.c	/	/	[276]
	In vitro(H9c2)	↑Cell viability, ↑beating rate, ↓LDH, ↑SOD	/	Oxidative stress	[277]
	In vitro(H9c2)	↑Cell viability, ↑beating rate, ↓LDH		Oxidative stress	[278]
	In vitro(H9c2)	↓Apoptosis, ↓p53, ↓caspase-3/9	/	Apoptosis	[279]
	In vivo(mice)	↓ST, ↓QT	/	/	[280]
	In vivo(mice)	↓ST	/	/	[281]
	In vivo(mice)	↑HF, ↑survival	/	/	[282]
	In vivo(mice)	↑Cell viability	/	Oxidative stress	[283]
	Phase I study	Indicated a feasible and safe dose up to 1, 500 mg/m^2			[284]
	Phase II study	monoHER enhanced DOX-induced cardiotoxicity			[285]
Silymarin	In vivo(rat)	↓NO	/	Oxidative stress	[286]
	In vivo(rat)	↓AST, ↓LDH, ↓CK, ↓LPx, ↓SOD, ↓CAT, ↓GSH-Px	/	Oxidative stress	[287]
	In vivo(mice)	↓ALT, ↓MDA, ↓DNA damage, ↓PARP, ↑Bcl-xL, ↓Cytochrome C, ↓p53	/	Oxidative stress, Apoptosis	[288]
	In vivo(mice)	↑cTnT, ↑cTnI, ↓γH2Ax, ↓DNA damage	↓Top2β	Top2β	[289]
	In vivo(rat)	↓LPO	/	Oxidative stress	[290]
	In vivo(rat)	↓CK	/	Oxidative stress, Inflammation	[291]
	In vivo(rat)	↓CPK, ↓LDH, ↓MDA, ↓creatinine	/	Oxidative stress	[292]
	Phase II study	Alleviated early doxorubicin-induced left ventricular systolic function disturbances			[293]

highlighting the importance of tailored administration schedules.[282] MonoHER also demonstrated anti-inflammatory properties by reducing the accumulation of Nepsilon-(carboxymethyl) lysine (CML), a marker of oxidative stress-induced inflammation. In murine models, monoHER pre-treatment significantly decreased the incidence of CML-positive cardiomyocytes and intramyocardial vessels.[283] These findings underline monoHER's role in modulating inflammation in DIC. Despite its efficacy, monoHER's cardioprotective potential is constrained by administration challenges, such as the need for parenteral delivery due to poor oral bioavailability. Additionally, while monoHER outperformed adenoviral CuZn-superoxide dismutase (CuZn-SOD) gene therapy, its pro-oxidant effects under certain conditions warrant further investigation to refine dosing strategies.[277]

Given the excellent anti-tumor and cardioprotection potential, monoHER was tested in clinical trials. In a phase I study to develop a safe and feasible dose in cancer patients treated with doxorubicin, the possible side effects and the pharmacokinetics of monoHER were evaluated in healthy volunteers. The results showed that The mean values of C (max) and AUC(infinity) were 360±69.3 microM and 6.8±2.1 micromol min/mL, which were comparable to the C (max) and AUC(infinity) observed under the protecting conditions in mice. Although the dose was escalated up to 1,500 mg/m^2, no serious side effects occurred during the entire study, indicating a feasible and safe dose to be evaluated in a phase I study.[284] Subsequently, the safety and efficacy was further tested on patients with metastatic cancer treated with DOX in a phase II study. Surprisingly, monoHER did not alleviate but enhance DIC with an intravenous infusion of 1,500 mg/m^2. However, the antitumour activity of DOX seemed better than expected. The investigators explained that the relatively high dose of monoHER may account for the observed lack of cardioprotection and the high response rate in patients with soft-tissue sarcoma, potentially through depletion of the GSH defense system in both cardiac and tumor tissues.[285]

Silymarin

Silymarin, a flavonolignan complex derived from *Silybum marianum*, has been widely investigated for its cardioprotective properties against DIC. These studies utilized diverse experimental approaches, including various animal models and analytical methods, to uncover the mechanisms underlying silymarin's protective effects. Notably, silymarin, particularly its active component silibinin, mitigates DIC through antioxidant, anti-apoptotic, and anti-inflammatory mechanisms. Evidence from both acute and chronic models highlights silymarin's efficacy. For instance, in male Wistar rats, oral administration of silymarin (60 mg/kg) over 12 days significantly alleviated oxidative stress, myocardial apoptosis, and functional impairments caused by DOX. The benefits were observed in improved ECG profiles, reduced lipid peroxidation markers such as MDA, and enhanced activities of antioxidant enzymes like SOD and GPx.[286,287] Histological analysis further corroborated these findings by revealing reduced myocardial necrosis and fibrosis.[287] A critical component of silymarin's protective action lies in its ability to maintain mitochondrial integrity. Histopathological and electron microscopic analyses revealed that silymarin prevented mitochondrial swelling and cytochrome c leakage, which are pivotal steps in apoptosis.[288] At the molecular level, silymarin exerts its cardioprotective effects by modulating key apoptotic and oxidative stress pathways. For instance, studies on BALB/c mice demonstrated that silymarin reduced DOX-induced cardiomyopathy by upregulating anti-apoptotic proteins (eg, Bcl-xL) and downregulating pro-apoptotic markers (eg, p53).[288] Additionally, silymarin inhibited DOX-induced Top2β-mediated DNA damage and decreased expression of γH2AX, improving mitochondrial function and preserving cardiac contractility.[289] Comparative studies with other flavonoids, such as quercetin, emphasized silymarin's unique protective mechanisms. While quercetin exhibited superior iron-chelating properties, silymarin's primary effects were attributed to its potent free radical scavenging and lipid peroxidation inhibition.[290] Moreover, combination therapy experiments, such as those involving verapamil, demonstrated that silymarin enhanced the cardioprotective effects of co-administered agents. For example, silymarin increased the verapamil dose required to induce toxic responses in DOX-treated models, showcasing its synergistic potential.[291] Beyond cardioprotection, silymarin demonstrated systemic benefits, as seen in studies involving albino rats. Pre-treatment with silymarin significantly reduced serum markers of cardiac and kidney injury, including NO, CPK, LDH and CK, creatinine and urea, while also normalizing renal MDA and GSH levels. These findings suggest that silymarin provides comprehensive protection, encompassing both the heart and other organs like the kidneys and liver.[286,287,292]

Based on the findings from preclinical studies, a perspective study examined the protective role of silymarin in early doxorubicin-induced cardiac dysfunction in children with acute lymphoblastic leukemia. As expected, silymarin was shown to alleviate early doxorubicin-induced left ventricular systolic function disturbances (LVEF, LVFS and S wave). Moreover, silymarin significantly decreased the level of troponin induced by doxorubicin. These findings supported the recommendation of silymarin as an adjuvant drug in early and late DIC.[293]

Challenges and Future Perspectives

While emerging evidence highlights the cardioprotective potential of flavonoids against DIC, critical challenges and knowledge gaps persist in translating preclinical findings to clinical applications. First, numerous studies remain descriptive, focusing on phenotypic observations (eg, reduced ROS, antioxidant enzymes and cardiac markers) without elucidating the underlying regulatory mechanisms of key signaling pathways such as ferroptosis and immunomodulation of the cardiac microenvironment. Current literature disproportionately emphasizes common subclasses such as flavones and flavonols, with limited exploration of other flavonoids. Beyond monoHER and silymarin, most compounds remain confined to cellular and animal studies, lacking comprehensive pharmacokinetic profiles and long-term safety assessments. Furthermore, the synergistic mechanisms between flavonoids and other natural products (eg, phenolic compounds) remain poorly characterized. Pharmacologically, many flavonoids (eg, quercetin, luteolin) face inherent limitations, including poor aqueous solubility and pronounced first-pass metabolism, which compromise bioavailability. Advanced strategies such as nanocarriers (eg, liposomes, polymeric micelles) and chemical modifications (eg, glycosylation) show promise in enhancing stability and myocardial targeting. Although nanotechnology has been developed to address the low bioavailability of flavonoids, current flavonoid delivery systems face significant challenges: (1) physical

instability and low drug loading capacity, primarily owing to the requisite abundance of pharmaceutical excipients, multi-step synthesis, and complex preparation methods; and (2) off-target toxicity resulting from the nonspecific biodistribution of oral formulations, byproduct generation, and incomplete carrier degradation.[296] Natural flavonoid extracts often exhibit compositional complexity, necessitating stringent quality control protocols to ensure batch-to-batch consistency in therapeutic efficacy. The combinatorial effects of flavonoids with conventional cardioprotective agents (eg, dexrazoxane) warrant rigorous validation to assess additive or synergistic benefits. Addressing these challenges will advance flavonoids as viable adjuvants in oncological regimens, balancing cardioprotection with chemotherapeutic efficacy. Additionally, the publication bias is unavoidable although articles concerning the potential of flavonoids against DIC are comprehensively reviewed. Most of the current evidence is derived from model organism such as H9c2 cells and mice which are not fully representative of adult human cardiomyocytes, and therefore is suggested to be further validated in human induced pluripotent stem cell-derived cardiomyocytes (hi-PSCMs).

Conclusion

Cardiotoxicity is a major limitation when considering dose escalation of DOX to enhance therapeutic efficacy. This review highlights 7 subclasses of flavonoids encompassing over 50 compounds that target oxidative stress, mitochondrial dysfunction, calcium imbalance, ferroptosis, inflammation and apoptotic pathways to mitigate doxorubicin-induced cardiotoxicity. Despite their promising preclinical efficacy, clinical translation remains hindered by challenges including suboptimal bioavailability, undefined drug-drug interactions, and insufficient clinical data. Future efforts which prioritize nanotechnology-driven delivery systems and structural optimization to improve bioavailability may enhance clinical applicability. Additionally, heterogeneity in study designs (eg, dosing, timing, treatment duration) complicates cross-study comparisons and hinders robust flavonoid prioritization. Crucially, most existing data lack justification for clinical applicability. To bridge this gap, critical next steps include: (1) Formulation optimization and PK/PD studies to define bioavailability and dosing regimens; (2) well-designed pre-clinical studies to determine the cardioprotection and anti-tumor efficacy of flavonoids based on tumor-cardiac dual models. Remarkably, quercetin emerges as the most promising candidate based on extensive preclinical evidence of multi-organ protection without compromising DOX efficacy, which deserves further clinical studies to confirm its clinical significance. Collectively, advancing flavonoids-based therapies from bench to bedside will provide safer adjunctive chemotherapeutic agents for cancer patients.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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