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Review

# Cardioprotective Effects of the Natural Antioxidant Epigallocatechin Gallate and Its Application to Drug Discovery

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## Abstract

Epigallocatechin gallate (EGCG), the principal constituent of catechins, has garnered considerable attention owing to its diverse health benefits. As a natural antioxidant and anti-inflammatory agent, EGCG has been shown in numerous studies to exert pronounced cardioprotective effects. Cardiovascular health is essential for human survival, yet it remains threatened by injuries associated with metabolic disorders, myocardial infarction, ischemia–reperfusion, and even general anesthesia. The development of a safe and effective cardioprotective agent would be of considerable value in diverse clinical settings. EGCG not only protects the coronary arteries but also attenuates adverse cardiac remodeling, prevents cardiomyocyte death, and enhances cardiac function, effects that have been consistently demonstrated in multiple animal models. Although clinical studies have confirmed the beneficial effects of EGCG on metabolic disorders, endothelial dysfunction, and cardiac hypertrophy, the sample sizes of these investigations remain relatively small. Moreover, numerous potential cardioprotective effects of EGCG under diverse clinical conditions remain to be systematically investigated. Further studies evaluating diverse dosing regimens of EGCG across various clinical contexts are required to establish its safety and efficacy and to facilitate its translation into clinical practice.

**Keywords:** epigallocatechin gallate; metabolic disorders; coronary artery disease; adverse cardiac remodeling; myocardial infarction; myocardial ischemia-reperfusion injury; cardiomyocyte injury; cardiac function

## 1. Introduction

Cardiac health is fundamental to overall human well-being, yet it is increasingly challenged by a variety of factors. Metabolic disorders, such as obesity, metabolic syndrome (MS), and type 2 diabetes mellitus (T2DM), have emerged as major health threats in the modern world [1]. Abnormalities in multiple metabolic components caused by these diseases impose persistent stress on the cardiovascular system, ultimately leading to coronary artery disease (CAD) and adverse cardiac remodeling [2]. Myocardial infarction (MI), the most severe clinical manifestation of CAD, affects approximately 3.8% of the global population under 60 years of age and up to 9.5% of those over 60 [3]. Another pressing issue associated with the rising incidence of MI is the lack of effective pharmacological interventions to prevent or treat myocardial ischemia–reperfusion injury (MIRI) during reperfusion therapy. In addition, with the widespread adoption of medical technology, the number of anesthesia cases has been rapidly increasing, rising annually by approximately 10% in China between 2015 and 2017 [4]. Consequently, the incidence of myocardial injury after non-cardiac surgery (MINS) is also expected to rise. MINS, defined as an elevation in cardiac troponin (cTn)

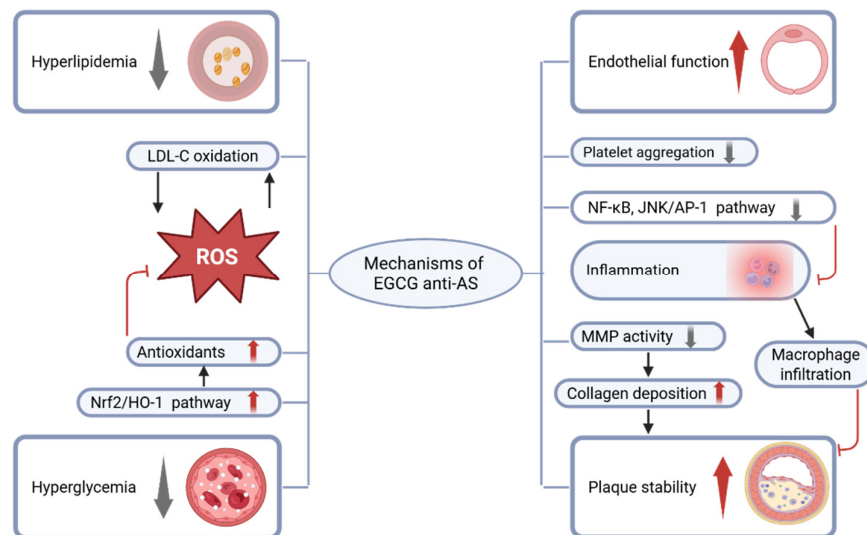
concentrations within 30 days postoperatively, is a frequent complication associated with increased postoperative mortality. Because most cases are asymptomatic, MINS is often overlooked [5].

Given the multiple threats to cardiac health, developing cardioprotective agents holds considerable clinical significance. Natural compounds, compared with synthetic substances, may be more suitable as therapeutic agents and play a pivotal role in drug development [6]. Tea has demonstrated a wide range of health benefits [7], for its rich content of polyphenolic compounds. Catechins are the main polyphenolic compounds in green tea (GT) and the unique polyphenolic compounds in other types of tea are mostly derived from their oxidation and fermentation processes [8]. EGCG, which represents 50–80% of the total catechins in GT, exhibits the strongest antioxidant capacity owing to its abundant hydroxyl groups [9]. As a natural anti-inflammatory and antioxidant substance, EGCG improves glucose and lipid metabolism [10], exerts preventive and therapeutic effects in CAD [11] and diabetic cardiomyopathy (DCM) [2]. Furthermore, EGCG demonstrates substantial potential in MI, MIRI [12], restrictive cardiomyopathy (RCM) [13], and heart failure (HF) [14], underscoring its broad cardioprotective effects. To bridge the gap between preclinical research and clinical application, we conducted this review. We summarize the cardioprotective effects of EGCG from four perspectives: coronary artery protection, inhibition of adverse cardiac remodeling, prevention of cardiomyocyte injury, and preservation of cardiac function. We also discuss its potential adverse reactions and future research directions, emphasized the significant impact of rational dosing regimens on outcomes, and provided specific experimental suggestions aiming to provide a foundation for the clinical translation of EGCG as a cardioprotective agent.

## 2. Cardioprotective Effects

### 2.1. Coronary Artery Protection

Atherosclerosis (AS) is a chronic inflammatory vascular disorder primarily induced by hyperlipidemia, hyperglycemia, smoking, and other risk factors. The primary pathological mechanism involves endothelial dysfunction and vascular wall injury induced by harmful stimuli, which promote lipid deposition and plaque formation, ultimately leading to CAD [15]. Chronic inflammation is critically involved in the initiation and progression of numerous diseases [16]. MS is also recognized as an inflammatory disorder [17]. EGCG, with potent antioxidant and anti-inflammatory activities, may play an essential role in protecting against MS [10]. The Nrf2/HO-1 signaling pathway, a major regulator of intracellular defense against oxidative stress, is regarded as an ideal target for alleviating endothelial cell injury [18]. EGCG not only attenuates oxidative stress via activation of the Nrf2/HO-1 pathway but also suppresses inflammatory responses in AS [19], thereby conferring endothelial protection. EGCG also exhibits anti-platelet aggregation effects, which are beneficial for preventing thrombosis. Matrix metalloproteinases (MMPs), key enzymes involved in extracellular matrix remodeling, are critical determinants of plaque stability. Numerous studies have indicated that polyphenols enhance plaque stability by suppressing MMP gene expression and enzymatic activity [20,21]. The main anti-AS mechanisms of EGCG are illustrated in **Figure 1**.



**Figure 1.** EGCG improves metabolic disorders and reduces the damaging effects of hyperlipidemia and hyperglycemia on blood vessels. At the same time, as a natural antioxidant, EGCG activates the Nrf2/HO-1 pathway, increases the levels of both enzymatic and non-enzymatic antioxidants in the body, inhibits the oxidation of low-density lipoprotein cholesterol (LDL-C) and the mutual promotion between ROS, reduces oxidative stress, and improves endothelial dysfunction. At the same time, it reduces inflammatory responses and inhibits macrophage infiltration in plaques by suppressing signaling pathways such as NF-κB and JNK/AP-1. In addition, EGCG inhibits the activity of matrix metalloproteinases (MMPs), increases collagen fiber content in plaques, inhibits platelet aggregation, thereby enhancing plaque stability.

### 2.1.1. Improve Metabolic Disorders

Clinical studies have demonstrated that long-term oral administration of EGCG exerts therapeutic effects on lipid abnormality (LA) associated with obesity [22–24] and smoking [25]. A clinical trial demonstrated that oral EGCG also has the effect of lowering blood pressure in obese patients [26]. Although another clinical trial reported no lipid-lowering effect of oral EGCG at 400 mg twice daily in obese patients [27] while noting a reduction in blood pressure, a systematic review demonstrated that daily oral intake of 107–856 mg of EGCG for 4–14 weeks significantly reduced serum low-density lipoprotein cholesterol (LDL-C) levels [28]. In patients with T2DM, a meta-analysis revealed that supplementation with green tea extract (GTE) for more than 8 weeks at doses exceeding 800 mg/day significantly reduced serum triglyceride (TG) concentrations [29]. Two clinical trials in T2DM patients with LA or obesity reported that daily oral administration of 1500 mg GTE ( $\approx$ 865 mg EGCG) for 16 weeks did not significantly improve insulin resistance or LA compared with placebo. However, both studies observed modest improvements in insulin resistance after 16 weeks of GTE treatment compared with baseline [30,31]. This outcome may be attributed to the bidirectional exacerbation between T2DM and LA, which resulted in more severe conditions in the study population [32], rendering the EGCG dosage and treatment duration insufficient. Extending EGCG administration to two months resulted in observable improvements in LA among T2DM patients [33]. In contrast, administration of EGCG in gestational diabetes mellitus (GDM), a condition less severe than T2DM, improved maternal glycemic indicators and reduced neonatal complications [34]. Although the anti-diabetic effects of EGCG have been validated in numerous preclinical studies [35–37], they remain inconclusive in humans. Across observational studies, the association between tea consumption and T2DM incidence has been inconsistent. Overall, drinking tea appears to confer some protection against T2DM, but the evidence remains inconclusive and may be confounded by lifestyle and dietary factors [38]. Habitual tea consumption provides only modest doses of EGCG, which are insufficient to override the influence of broader lifestyle and dietary factors. Although

current clinical trials have not demonstrated significant anti-diabetic efficacy of EGCG, they have reported improvements in LA among T2DM patients, reductions in blood pressure [33], and amelioration of arterial stiffness [39], all of which are beneficial for CAD. The clinical trial findings regarding the coronary protective effects of EGCG and its inhibition of adverse cardiac remodeling are summarized in **Table 1**.

**Table 1.** A summary of clinical trials on the cardioprotective effects of EGCG.

Study population	Dose	Effect	References
88 obese male patients aged 40-65 years	400 mg of EGCG (po, bid) for 8 weeks	DBP ↓ NS between groups: HOMA-IR index, OGTT TG, TC, HDL-C, LDL-C SBP, DBP ↓	[27]
56 obese patients with hypertension	379 mg of GTE (po, qd) for 3 months	HOMA-IR index, FBG ↓ TNF- $\alpha$ , CRP ↓ T-AOC ↑ TC, TG, LDL-C ↓ HDL-C ↑	[22]
102 women with central obesity	856.8mg of EGCG (po, qd) for 12 weeks	TC, LDL-C ↓	[23]
30 obese patients	150mg of EGCG (po, bid) for 8 weeks	Serum kisspeptin, TG ↓	[24]
30 obese patients	150mg of EGCG (po, bid) for 8 weeks	SBP, DBP, MAP ↓	[26]
68 T2DM patients with obesity	1,500 mg of GTE (po, qd) for 16 weeks (Supplement to routine medication)	NS between groups: HOMA-IR index, FBG, HbA1c Within GTE group: Compared to baseline HbA1c ↓	[30]
77 T2DM patients with LA	500 mg of GTE (po, tid) for 16 weeks (Supplement to routine medication)	NS between groups: HOMA-IR index, FBG, HbA1c TG, TC, HDL-C, LDL-C Within GTE group: Compared to baseline GLP-1 ↑ HOMA-IR ↓	[31]
326 pregnant women diagnosed with GDM during third trimester until full term	500 mg of EGCG (po, qd)	Maternal diabetic parameters ↑ Cases of neonatal complications ↓	[34]
20 T2DM patients	400 mg of GTE (po, qd) for 12 weeks	Improved arterial stiffness	[39]
50 T2DM patients	300 mg of EGCG (po, bid) for 2 months (Supplement to routine medication)	MAP, DBP ↓ TC, TG, AIP ↓ T-AOC ↑	[33]
120 South Indian male smokers	100 ml of GT (po, tid) for 1 year	Improved LA	[25]
52 patients with early AS	30 ml olive oil with 280 mg of EGCG	Endothelial function ↑	[40]

42 CAD patients	(po, qd) for 4 months (Supplement to routine medication) 150 mg of EGCG (po, bid) for 2 weeks (Supplement to routine medication) GT and/or GTE (Exposure factors)	Endothelial function ↑	[41]
19 patients with ATTR-CM	for 1 year (Supplement to routine medication) 600 mg of EGCG (po, qd) for 1 year (Supplement to routine medication)	Left ventricular mass ↓ TC, LDL-C ↓	[42]
25 male patients with wtATTR-CM	(Supplement to routine medication)	Left ventricular mass ↓ Extracellular volume fraction ↓ TC ↓	[13,43]

### 2.1.2. Alleviate Endothelial Dysfunction

The vascular endothelium is pivotal in regulating vascular homeostasis, and preserving its vasodilatory, anti-inflammatory, antithrombotic, and antiproliferative functions is essential for mitigating cardiovascular risk. Notably, the endothelial protective effects of EGCG have been confirmed in clinical trials involving patients with early AS or CAD [40,41]. All preclinical studies investigating the coronary protective effects and the inhibition of adverse cardiac remodeling by EGCG are summarized in **Table 2**. In vivo animal studies demonstrated that EGCG activated the Nrf2/HO-1 pathway to attenuate oxidative stress, inhibited lipid peroxide formation, suppressed NF- $\kappa$ B signaling, and limited the release of inflammatory mediators, thereby conferring endothelial protection in high-fat diet-fed mice [44–46]. Furthermore, human primary T cells cultured in vitro and pretreated with EGCG exhibited marked reductions in AP-1 activity and inflammatory cytokine secretion upon stimulation [47]. Collectively, the potent antioxidant and anti-inflammatory properties of EGCG safeguard endothelial integrity, a mechanism critical for attenuating the progression of CAD.

**Table 2.** A summary of preclinical studies on the protective effects of EGCG on atherosclerosis and adverse cardiac remodeling with different dosing regimens in various injury models.

Injury Models	Dosage regimen	Results	References
Atherogenic diet for 45 days in male Wistar rats	EGCG 100 mg/kg (ip, qd) for the last 14 days	CRP, ESR ↓	[44]
High-fat diet for 15 weeks	Drinking water with EGCG (0.2 g/L) for 7 weeks	AS areas ↓ CRP, IL-8, MCP-1 ↓ HO-1 ↑ oxidized LDL-C ↓	[45]
P. gingivalis (iv, tiw) for 3 weeks in ApoE-deficient mice	EGCG 100 mg/kg (ip, qd) for 6/12 days	TC, TG, LDL-C ↓ HDL-C ↑ Antioxidants ↑ Lipid peroxidation ↓	[46]
High-fat diet for 16 weeks in ApoE-deficient mice	EGCG 10 mg/kg (ip, qd) for 16 weeks	TNF- $\alpha$ , IL-6, MCP-1, INF- $\gamma$ ↓ EMMPRIN, MMP-2, MMP-9 ↓ Plaque stability ↑	[48]

High-fat diet for 6 weeks in ApoE-deficient mice	EGCG 10, 20, 40 mg/kg (po, qd) for 6 weeks	TC, TG, LDL-C, ↓ HDL-C ↑ VEGFA, MMP-2 ↓ SOD, Nrf2/HO-1 pathway ↑ ROS ↓	[49]
T2DM in db/db mice	Diet with EGCG (10 g/ kg) for 10 weeks	FBG ↓ Plasma insulin ↑ Number of pancreatic islets ↑ HOMA-IR index, FBG, HbA1c ↓ TG, TC, LDL-C, VLDL-C ↓ HDL-C ↑ SOD, CAT, GSH ↑ ROS ↓	[35]
NAM 100 mg/kg (ip) 20 min later STZ 55 mg/kg (ip) in male Wistar rats	After induction of DM EGCG 2 mg/kg (po, qod) for 1 month	IL-1β, IL-6, TNF-α, ICAM-1, VCAM-1 ↓ cTnT, CK-MB, LDH, AST ↓ Histopathological injury ↓ Apoptosis ↓ Fibrosis area ↓	[36]
STZ 65 mg/kg (ip) in male SD rats	After induction of DM EGCG 10, 20, 40 mg/kg (po, qd) for 12 weeks	FBG ↓ TG, TC, LDL-C ↓ HDL-C ↑ Fibrosis area, COL-I, COL-III ↓	[37]
Senium (24-26 months of age) in albino Wistar rats	EGCG 200 mg/kg for 30 days	Nrf2 ↑ ROS ↓ NF-κB ↓ TGFβ, TNFα ↓ Apoptosis ↓ COL ↓	[50]
AAC for 4 weeks in male SD rats	EGCG 25, 50 mg/kg (po, qd) for 4 weeks	NF-κB activation, CTGF ↓ Fibrosis area ↓	[51]
TAC for 4 weeks in male C57BL/6 mice	EGCG 20, 40, 80 mg/kg (po, qd) for 4 weeks	HW/BW, HW/TL, COL ↓ AKT/mTOR pathway ↓	[52]
COL (10 μg/mL) for 5 min with washed platelets from male SD rats	Preincubated with 1, 5, 10, 30, 50 μM EGCG for 3 min	Platelet aggregation ↓	[53]
100 nM Ang II for 24 h with CFs of adult rats	Preincubated with 1, 10 μM EGCG for 1 h	CFs proliferation ↓ NF-κB, CTGF ↓ COL-I, COL-III ↓	[51]
10nM Ang II for 4h with CFs of adult rats	At the same time EGCG 1, 10,100 μM for 4h	JNK/AP-1 ↓ Endoglin ↓ CFs proliferation ↓	[54]
ADP 6.5 μM or COL 3.2μg/ml for 6 min with blood samples from people taking antiplatelet drugs	EGCG 50, 100, 200 μM preincubated for 30 min	Platelet aggregation ↓	[55]
Human primary T cells incubated with P/I for 20 h	EGCG 10, 20 μM preincubated for 4 h	AP-1 binding activity ↓ IL-2, IL-4, INF-γ, TNF-α ↓	[47]
TGF-β2 10 ng/mL IL-1β 1 ng/mL for 24 h with HUVECs	After injury EGCG 1, 5, 10 μM for 24h	ROS ↓ NF-κB, SMAD pathways ↓ RhoA ↓ Cell migration ↓ EndMT ↓	[56]

10 mM $\beta$ -GP and 3 mM CaCl <sub>2</sub> with HASMCs	EGCG 20, 30 $\mu$ M	JunB ↓ Osteogenic differentiation ↓ Mineral deposition ↓	[57]
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### 2.1.3. Prevent Coronary Thrombosis

In vitro studies have demonstrated that EGCG suppresses platelet aggregation [53,55], thereby contributing to thrombosis prevention. Furthermore, as nearly 76% of fatal coronary thrombi are triggered by plaque rupture, maintaining plaque stability is of critical importance for patients with AS. In AS mouse models, EGCG exhibited anti-inflammatory, antioxidant, and lipid-lowering effects, and further suppressed MMP-2 and MMP-9 activity in plaque tissues, reduced macrophage infiltration, increased smooth muscle cell and collagen content, thickened the fibrous cap, and ultimately enhanced plaque stability [48,49].

## 2.2. Inhibition of Adverse Cardiac Remodeling

The reconstruction of the cardiac extracellular matrix requires a finely regulated balance. Moderate fibrotic repair preserves cardiac structural stability, whereas excessive collagen deposition impairs cardiac function. Adverse cardiac remodeling occurs in multiple pathologies, including post-MI [58], DCM, HF, RCM, hypertrophic cardiomyopathy (HCM). Consequently, inhibiting adverse cardiac remodeling represents a critical therapeutic strategy and objective.

### 2.2.1. Inhibit Collagen Deposition

In vitro studies have demonstrated that EGCG suppresses the proliferation of cardiac fibroblasts (CFs) and collagen (COL) deposition, potentially by downregulating the NF- $\kappa$ B pathway to decrease connective tissue growth factor (CTGF) expression [51], or by inhibiting the JNK/AP-1 pathway to attenuate endoglin expression [54]. Beyond its actions on CFs, EGCG also inhibits endothelial-to-mesenchymal transition (EndMT) and calcium deposition in vascular smooth muscle cells by suppressing NF- $\kappa$ B signaling and inactivating JunB [56,57]. In diabetic mouse models, EGCG improved glucose and lipid metabolism, reduced cardiomyocyte apoptosis, and decreased the extent of cardiac fibrosis [36,37]. Similarly, in vivo experiments in aging [50] and HF mouse models [51,52], also demonstrated reduced COL deposition following EGCG treatment.

### 2.2.2. Inhibit Amyloid Deposition

Transthyretin is the most common precursor protein of hereditary amyloidosis, and its cardiac deposition leads to RCM. In contrast to the hereditary form, no characteristic mutations in the transthyretin gene are detected in patients with wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM), a condition predominantly affecting elderly individuals, and the underlying pathogenic mechanisms remain to be elucidated. In clinical trials, long-term oral administration of EGCG reduced left ventricular mass in patients with wtATTR-CM [13,42]. Imaging analyses further revealed that the reduction in left ventricular mass originated not from CMs but from the extracellular matrix [43]. These findings suggest that EGCG may exert therapeutic benefits in wtATTR-CM by modulating extracellular matrix remodeling rather than directly affecting CMs.

## 2.3. Prevention of Cardiomyocyte Injury

MI and MIRI expose CMs to severe oxidative stress and inflammatory responses [59], which consequently result in cardiomyocyte injury, mitochondrial damage, pro-apoptotic factor release, and apoptosis [60]. EGCG exerts potent antioxidant, anti-inflammatory, and anti-apoptotic effects [61], showing great potential for application in MI and MIRI. Beyond apoptosis, other forms of regulated cell death (RCD) also have increasingly attracted attention in the context of MI and MIRI [62,63]. Autophagy constitutes a crucial metabolic pathway that supports cell survival under conditions of nutrient deprivation, hypoxia, or oxidative stress. Excessive autophagy, however,

aggravates cellular dysfunction and induces RCD [64]. Preclinical studies have demonstrated that MI and MIRI suppress PI3K/Akt signaling pathway [65] and induce excessive autophagy in CMs, thereby increasing RCD, whereas EGCG administration markedly reversed these pathological responses. A meta-analysis confirmed the cardioprotective effects of EGCG against MI and MIRI in small-animal models [12]. However, there are currently no clinical studies to validate the efficacy of EGCG in MI and MIRI, and all preclinical studies on its protective effects against cardiomyocyte injury in different diseases are summarized in **Table 3**.

**Table 3.** A summary of preclinical studies on the protective effects of EGCG on cardiomyocyte injury with different dosing regimens in various injury models.

Injury Models	Dosage regimen	Results	References
CPB Bypass-time for 90 min Reperfusion for 2 h in domestic piglets (10–15 kg)	Before CPB EGCG 10 mg/kg (iv) After CPB EGCG 10 mg/kg (iv)	CK ↓ Nitrosative and oxidative stress ↓ Inflammation ↓ Apoptosis ↓	[66]
ISO 100 mg/kg (sc, qd) for 2 days in male Wistar rats	After induction of MI EGCG 10, 20, 30 mg/kg (po, qd) for 21 days	LDL-C, VLDL-C ↓ HDL-C ↑ AIP ↓ GSH, VC, VE, CER ↑ SOD, CAT ↑ MDA ↓ Mitochondrial damage ↓ Lysosomal enzymes ↓ CK, CK-MB, LDH, AST, ALT ↓ Histopathological injury ↓ HW, HW/BW ↓	[67–72]
ISO 100 mg/kg (sc, qd) for 2 days in male Wistar rats	Before induction of MI EGCG 15 mg/kg (ip, qd) for 7 days	TC, TG, LDL-C ↓ HDL-C ↑ SOD, CAT ↑ MDA ↓ TNF-α ↓ CK-MB, LDH, ALT, ALP, cTnT ↓ DNA damage, Apoptosis ↓	[101]
LADO for 30 min Reperfusion for 2 h in male SD rats	5 min before reperfusion EGCG 10 mg/kg (iv)	PI3K/AKT pathway ↑ p38, JNK ↓ Infarct size ↓	[73]
LADO for 30 min Reperfusion for 2 h in male Wistar rats	5 min before reperfusion EGCG 10 mg/kg (iv)	PI3K/AKT pathway ↑ Plasma mtDNA, TNF-α, IL-6, IL-8 ↓ Incidence of ventricular arrhythmia ↓ Infarct size ↓	[74]
LADO for 30 min Reperfusion for 12 h in SD rats	30 min before ischemia EGCG 10 mg/kg (iv)	PI3K/AKT pathway ↑ miR-384 ↑ Beclin-1, Excessive autophagy ↓ cTnI ↓ Infarct size ↓ LncRNA Gm4419 ↓ ERK1/2 ↓	[75]
LADO for 45 min Reperfusion for 3 h in male C57BL/6 mice	Before injury EGCG 250 mg/kg (po, qd) for 10 days	Excessive autophagy ↓ Apoptosis ↓ Histopathological injury ↓ Infarct size ↓ Self-cleavage of OMA1 ↓	[76]
H <sub>2</sub> O <sub>2</sub> or HRI with MEFs or CMs of neonatal mice	Before injury EGCG 20, 30, 40 μM for 1-3 h	Proteolysis of OPA1 ↓ Mitochondrial function ↑ Mitochondrial morphology ↑ Apoptosis ↓	[77]
miR30a knockdown cells Hypoxia for 24 h	Exosomes from EGCG-Treated CMs	miR30a ↑ Cell viability ↑	[78]

H <sub>2</sub> O <sub>2</sub> 100 μM for 24 h with CMs of neonatal mice	EGCG (The dose is unknown)	LncRNA Gm4419 ↓ ERK1/2 ↓ Excessive autophagy ↓ Apoptosis ↓ Cell viability ↑ LDH ↓	[76]
HL-1 cells Hypoxia for 18 h	Before hypoxia EGCG 5, 25 μM for 8h	GSH, GPX4 ↑ ROS ↓ miR-450b-5p ↑ ACSL4, Ferroptosis ↓ Cell viability ↓	[79]
H9c2 cells in 30 mM glucose Hypoxia for 2 h Reoxygenation for 4 h	Before injury EGCG 20 μM for 24 h	SIRT1 ↑ Mn-SOD ↑ MDA ↓ Apoptosis ↓ Cell viability ↑ LDH ↓	[80]
H9c2 cells Hypoxia for 6 h Reoxygenation for 12h	Before injury EGCG 6.25, 25 μM for 4 h	miR30a ↑ p53 ↓ Apoptosis ↓ CK-MB, LDH ↓ Cell viability ↑ ATP ↑	[78]
H9c2 cells Hypoxia for 6 h Reoxygenation for 12h	Before injury EGCG 25 μM for 4 h	PI3K/AKT pathway ↑ miR-384 ↑ Beclin-1, Excessive autophagy ↓ cTnI ↓ Cell viability ↑	[75]
H9c2 cells Hypoxia for 6 h Reoxygenation for 12h	Before injury EGCG 8 mg/L for 24 h	ROS ↓ ATG4C ↑ Excessive autophagy ↓ ATP ↑ Apoptosis ↓ Cell viability ↑	[81]
HL-1 cells Hypoxia for 2, 4, 8, 12 h Reoxygenation for 24h	Before injury 5, 10, 20, 40, 80, 100 μM of EGCG for 3h	LncRNA MEG3 ↓ TAF15 in cytoplasm ↓ AIM2 mRNA stability ↓ Pyroptosis ↓ Cell death rate ↓ Cell viability ↑ ROS, MDA ↓	[82]
H9c2 cells Hypoxia for 3 h Reoxygenation for 2 h	Before injury EGCG 10 μM for 48 h	14-3-3η ↑ Excessive autophagy ↓ Ferroptosis, Apoptosis ↓ Cell viability ↑ LDH ↓	[83]

### 2.3.1. Alleviate Oxidative Stress and Inflammatory Responses

Although the global ischemic injury induced by hypothermic cardiac arrest during cardiopulmonary bypass (CPB) is less severe than that observed in MI or MIRI and typically does not result in irreversible cardiac dysfunction, CMs are nevertheless exposed to oxidative stress and inflammatory damage, leading to apoptosis and elevated plasma myocardial enzyme levels, a condition partially resembling MINS. In a large-animal model simulating CPB injury, supplementation of the cardioplegic solution with EGCG alleviated cardiomyocyte injury [66]. Subcutaneous injection of isoproterenol (ISO) to induce MI in mice resulted in LA, heightened oxidative stress and inflammation, and subsequent cardiomyocyte injury. EGCG administration, whether before or after MI induction, significantly improved LA, lowered the atherogenic index of plasma (AIP), and elevated antioxidant defenses—including enzymatic antioxidants such as superoxide dismutase (SOD) and catalase (CAT), as well as non-enzymatic antioxidants such as vitamin C, vitamin E, and ceruloplasmin—in mice. These effects collectively reduced reactive oxygen species (ROS) and malondialdehyde (MDA) levels, decreased tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) expression, and ultimately alleviated cardiomyocyte injury [67–72,84].

### 2.3.2. Alleviate Mitochondrial Dysfunction

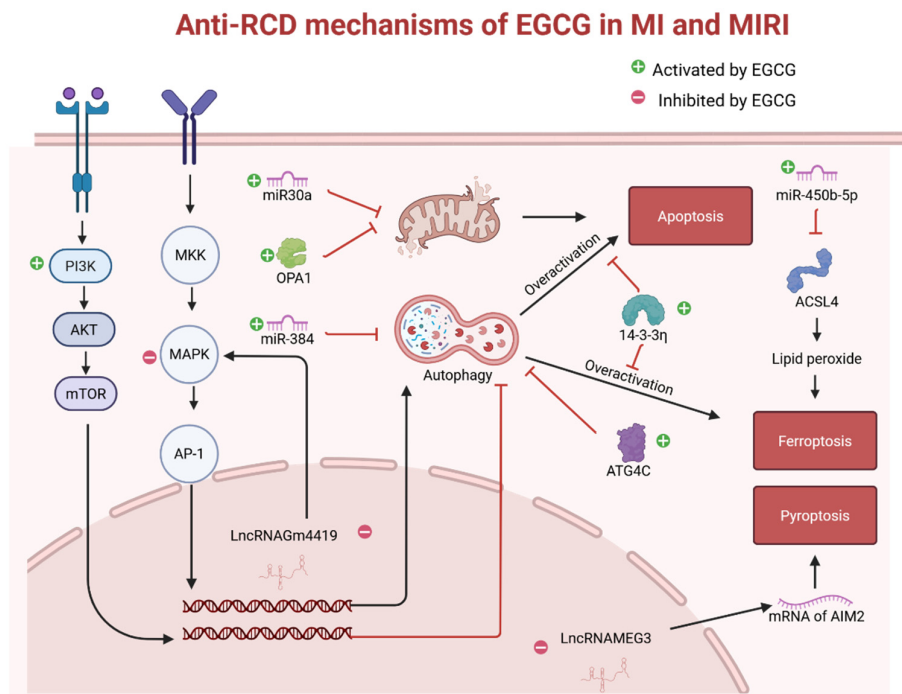
Preserving mitochondrial structure and function not only ensures energy supply for cellular activities but also constitutes a fundamental mechanism for preventing the initiation of mitochondrial apoptosis and sustaining cell survival. Beyond the classical roles of Bcl-2 family proteins and the pro-apoptotic factor cytochrome c, EGCG mitigates mitochondrial injury and its downstream consequences through additional molecular pathways. In MI rat models, the activity of tricarboxylic acid cycle enzymes and mitochondrial respiratory chain marker enzymes in CMs was markedly reduced, whereas EGCG pretreatment significantly attenuated these alterations and preserved mitochondrial function [69]. Intravenous administration of EGCG (10 mg/kg) 5 minutes before reperfusion significantly reduced plasma levels of mitochondrial DNA (mtDNA) and inflammatory cytokines—including TNF- $\alpha$ , IL-6, and IL-8—in MIRI mice. Moreover, plasma mtDNA levels positively correlated with TNF- $\alpha$ , IL-6, and IL-8, suggesting that mtDNA may function as a pro-inflammatory mediator [74]. OPA1 is a key regulator of inner mitochondrial membrane fusion and cristae maintenance. OMA1, a metalloendopeptidase, initiates OPA1 proteolysis, and its short autolytic form exhibits hydrolytic activity. EGCG directly interacted with OMA1 and strongly inhibited its self-cleavage, thereby attenuating OPA1 proteolysis and suppressing mitochondrial apoptosis [77].

### 2.3.3. Activate the Protective PI3K/Akt Pathway

The PI3K/Akt signaling pathway serves as an intrinsic regulatory mechanism that promotes cell survival under harmful external stimuli, engaging multiple downstream targets and influencing diverse cellular functions. Multiple studies have demonstrated that the cardioprotective effects of EGCG in MI and MIRI are mediated through activation of this pathway, whereas pharmacological inhibition of PI3K/Akt signaling abolishes the protective effects of EGCG [73–75].

### 2.3.4. Inhibit Regulated Cell Death

In addition to oxidative stress, inflammatory responses, and mitochondrial damage, MI and MIRI also induce excessive autophagy in CMs, leading to functional impairment and increased apoptosis. The inhibitory effects of EGCG on excessive autophagy and apoptosis have been confirmed in multiple studies [75,76,81]. MicroRNA-30a (miR-30a) inhibits apoptosis by regulating gene expression, and EGCG treatment in MI mice upregulated miR-30a expression in CMs. Notably, miR-30a can also be transferred to neighboring CMs via exosomes, thereby exerting protective effects [78]. In recent years, beyond apoptosis, which has been extensively characterized, other forms of RCD—including ferroptosis and pyroptosis—have been recognized as critical contributors to MI and MIRI. Studies have shown that EGCG inhibits ferroptosis in CMs by upregulating 14-3-3 $\eta$  protein [83] and miR-450b-5p [79] in mice, and suppresses pyroptosis by downregulating long non-coding RNA (LncRNA) MEG3, which reduces the stability of AIM2 mRNA [82]. Collectively, through multiple pathways, EGCG suppresses RCD in CMs and enhances their survival, and the main anti-RCD mechanisms of EGCG in MI and MIRI are illustrated in **Figure 2**.



**Figure 2.** In MI and MIRI, cardiomyocytes often exhibit impaired PI3K signaling pathways and overactivation of MAPK pathways, leading to excessive autophagy and the induction of regulated cell death (RCD). EGCG mitigates this phenomenon through the mediation of miR-384, LncRNAGm4419, 14-3-3 $\eta$  protein, and ATG4C protein. In addition, EGCG increases the expression level of miR-30a, inhibits the hydrolysis of OPA1, and thereby suppresses mitochondrial apoptosis. EGCG reduces ACSL4 protein expression by increasing the expression level of miR-450b-5p, thereby inhibiting ferroptosis; and it reduces the stability of AIM2 mRNA by lowering the expression level of LncRNAMEG3, thereby inhibiting pyroptosis.

#### 2.4. Preservation of Cardiac Function

Cardiac function is regulated by multiple factors. The inhibitory effects of EGCG on adverse remodeling, its preservation of mitochondrial function, and its suppression of RCD in MI and MIRI collectively contribute to the attenuation of cardiac dysfunction. Beyond MI and MIRI, *in vivo* mouse studies have validated the protective effects of long-term oral EGCG on cardiac function in aging, manganese superoxide dismutase (Mn-SOD) deficient, and troponin mutation related RCM models [85–87]. Long-term oral administration of EGCG also enhanced tolerance to MIRI in T2DM mice [80], and spontaneously hypertensive rats (SHR) [88], thereby mitigating cardiac dysfunction. Furthermore, EGCG directly interacts with cTn, modulates thin-filament function, increases ATP content, and enhances calcium transients, thereby improving contractile function at the single-cell level. All preclinical studies on the cardioprotective effects of EGCG on cardiac function are summarized in **Table 4**.

**Table 4.** A summary of preclinical studies on the protective effects of EGCG on cardiac function with different dosing regimens in various injury models.

Injury Models	Dosage regimen	Results	References
Healthy male Wistar rats (po, qd)	0.12 mg of EGCG for 28 days	Mitochondrial function $\uparrow$	[89]
		ATP $\uparrow$	
		Cardiomyocyte mechanics $\uparrow$	
Transgenic mice (cTnI-R193H)	EGCG 50 mg/kg (ip, qd)	Diastolic function $\uparrow$	[85]

Senium C57BL/6 mice (16-18 months old)	for 3 months At the age of 16 months EGCG 50 mg/kg (ip, qd) for 8 weeks	Diastolic function ↑ HDAC1, HDAC3 ↓ cTnI ↑	[86]
Mn-SOD-deficient mice	At the age of 8 week EGCG 10, 100mg/L in drinking water for 8 weeks	Survival rate ↑ Cardiac dilatation ↓ Cardiac contraction ↑ Oxidative stress, Free fatty acids ↓ Telomerase activity ↓ Telomere length ↑ FBG ↓	[87]
High-fat diet for 4 weeks STZ 30 mg/kg (ip) for 2 doses in 1 week in male SD rats	After induction of DM EGCG 40, 80 mg/ kg (po, qd) for 8 weeks	CK-MB, cTnI ↓ Histopathological injury ↓ Autophagy, MMP2, MMP9 ↑ Fibrosis area, COL-I, COL-III ↓ LVSP, ±dp/dt max ↑ LVEDP ↓ Histopathological injury ↓ BNP ↓ Oxidative stress ↓	[90]
TAC for 4 weeks in C57BL/6 mice	EGCG 10 mg/kg (ip, qd) for 4 weeks	Inflammation ↓ Apoptosis ↓ LVEDD, LVESD ↓ LVEF ↑ TGF-β1/smad3 pathway ↓ COL-I, COL-III ↓	[14]
TAC for 12 weeks in C57BL/6 mice	After TAC EGCG 50 mg/kg (ip, qd) for 12 weeks	Preventive effect on HF SERCA2a ↑	[91]
AAC for 4 weeks in rats	After AAC EGCG (25, 50, 100 mg/kg/day) for 4 weeks	GRK2 ↓ β1-AR ↑ HW/BW, Posterior wall thickness ↓ LVSP, ±dp/dt max ↑ LVEDP ↓ Histopathological injury ↓	[92]
TAC for 12 weeks in mice	EGCG 50 mg/kg (ip, qd) for 12 weeks	HDAC5 ↓ Cardiac enlargement ↓ Cardiac function ↑	[93]
AAC for 16 weeks in male SD rats	8 weeks after AAC EGCG 100 mg/kg (ip, qd) for 8 weeks	Cardiac function ↑ Myocardial hypertrophy, fibrosis ↓ Mitochondrial function ↑	[94]
LADO for 12h in male SD rats	2h before induction of MI EGCG 10 mg/kg (iv)	miR30a levels ↑ CK-MB, cTnI ↓ Histopathological injury ↓ Excessive autophagy ↓ Apoptosis ↓ LVEF, LVSP, ±dp/dt max ↑ LVEDP ↓	[78]
LADO for 18h in C57BL/6 mice	30 min before induction of MI EGCG 5, 10, 20 mg/kg (iv)	SOD ↑ MDA ↓ miR-450b-5p ↑ ACSL4, Ferroptosis ↓ LVEDD, LVESD ↓ LVEF, FS ↑	[79]
LADO for 4 weeks	After induction of MI EGCG 50 mg/kg	CK-MB, LDH ↓ Histopathological injury ↓	[82]

in C57BL/6 mice	(po, qd) for 4 weeks	LncRNA MEG3 ↓ Pyroptosis ↓ Cell death rate ↓ Infarct size ↓ LVEF ↑	
LADO for 14 days in adult Wistar rats	After induction of MI EGCG 50 mg/kg (po, qd) for 14 days	Endoglin ↓ HW/BW, Fibrosis area ↓ LVEDD, LVESD ↓ MAP, FS ↑	[54]
LADO for 4 weeks in C57BL/6 mice	After induction of MI EGCG 50 mg/kg (po, qd) for 1 week	1 week after MI: Snail (EndMT marker) ↓ MMP-2, MMP-9 ↓ COL-I, COL-III ↓ 4 weeks after MI: Apoptosis ↓ Infarct size ↓ Fibrosis area ↓ Capillary density ↑ LVEF ↑ SIRT1 ↑	[56]
LADO for 30 min Reperfusion for 2 h in SD rats with DM	Before injury EGCG 100 mg/kg (po, qd) for 2 weeks	Mn-SOD ↑ MDA ↓ LDH ↓ Apoptosis ↓ Infarct size ↓ Fibrosis area ↓ LVSP, ±dp/dt max ↑ PI3K/AKT pathway ↑	[80]
LADO for 30 min Reperfusion for 2 h In male SD rats	10 min before reperfusion EGCG 10 mg/kg (iv)	Excessive autophagy ↓ CK-MB, LDH ↓ Nitric oxide ↑ Apoptosis ↓ Infarct size ↓ LVSP, ±dp/dt max ↑ LVEDP ↓ miR30a ↑ p53 ↓ Apoptosis ↓	[95]
LADO for 30 min Reperfusion for 12 h in SD rats	30 min before ischemia EGCG 10, 20 mg/kg (iv)	CK-MB, LDH ↓ Histopathological injury ↓ ATP ↑ LVEF, LVSP, ±dp/dt max ↑ LVEDP ↓ MDA ↓ Ferroptosis ↓	[96]
LADO for 60 min Reperfusion for 2 h in C57BL/6 mice	Before injury EGCG 20 mg/kg (po, qd) for 6 weeks	CK-MB, LDH ↓ Histopathological injury ↓ Infarct size ↓ LVEF ↑	[83]
LIHPS for hearts of male Wistar rats	EGCG 1, 4 μM in perfusate	LVSP, ±dp/dt max ↑	[97]
LIHPS for hearts of Chinchilla rabbits Cardioplegia for 90 min Reperfusion for 1 h	At the same time of cardioplegia EGCG 20 μM in cardioplegic solutions for 90 min	Nitrosative and oxidative stress ↓ Apoptosis ↓ ATP ↑ LVSP ↑	[98]
LIHPS for hearts of male SHR Ischemia for 30 min	Before injury EGCG 200 mg/kg (po, qd) for 3 weeks	Coronary flow ↑ Infarct size ↓ LVDP ↑ LVEDP ↓	[88]

Reperfusion for 2 h LIHPS for hearts of guinea pigs Ischemia for 40 min Reperfusion for 40 min	4 min before injury EGCG 30 $\mu$ M in perfusate	Mitochondrial Ca <sup>2+</sup> elevation ↓ Apoptosis ↓ ATP ↑ LVEDP ↓	[99]
LIHPS for hearts of male Wistar rats Ischemia for 30 min Reperfusion for 2 h	10 min before ischemia EGCG 1, 10 $\mu$ M in perfusate for 40 min	Infarct size ↓ LVDP, $\pm$ dp/dt max NS Mitochondrial KATP activity ↑	[100]
LIHPS for hearts of male Wistar rats Ischemia for 30 min Reperfusion for 2 h	5 min before reperfusion EGCG 1, 10 $\mu$ M in perfusate for 35 min	Infarct size ↓ LVDP, $\pm$ dp/dt max ↑	[101]
LIHPS for hearts of male SD rats Ischemia for 20 min Reperfusion for 2 h	10 min before injury EGCG 5 $\mu$ M in perfusate for 130 min	Mn-SOD, Cu/Zn-SOD ↑ Lipid peroxides ↓ Apoptosis ↓ Infarct size ↓ LVDP, $\pm$ dp/dt max ↑ LVEDP ↓	[102]
CMs of adult rats	EGCG 2.5, 5 $\mu$ M	Calcium transient ↑ FS ↑	[97]
CMs of C57BL/6 mice	EGCG 10nM-100 $\mu$ M	Calcium transient ↑	[103]
Human cTn subunits with cTnT- $\Delta$ 160E mutation	EGCG 3 $\mu$ M	Bind to the C-lobe of cTnC Binding of cTnI to cTnC ↑ Ca <sup>2+</sup> sensitivity in myofilaments ↓	[104]
CMs of transgenic mice (cTnI-R193H)	EGCG 5 $\mu$ M	Ca <sup>2+</sup> decay, Sarcomere relaxation ↑	[85]
cTnT with mutations associated with HCM	EGCG 100 $\mu$ M	Restore the coupling between Ca <sup>2+</sup> and cTnT	[105]
Reconstituted TF with cTnC-G34S or cTnI-D127Y mutations	EGCG 20 $\mu$ M	Aggregation and elongation of TF ↑ Maximal myosin-S1-ATPase activity ↑ Ca <sup>2+</sup> sensitivity in myofilaments ↓	[106]

#### 2.4.1. Better Cardiac Structure

Adverse cardiac remodeling results in myocardial fibrosis and reduced compliance. The inhibitory effects of EGCG on adverse cardiac remodeling have been discussed earlier, including clinical trials evaluating its ability to inhibit transthyretin deposition; however, improvement in cardiac function was not the primary endpoint. Numerous *in vivo* mouse studies have demonstrated that long-term EGCG treatment ameliorated myocardial fibrosis and improved cardiac function in models of T2DM [90], HF [14,91–94], and post-MI [54,56].

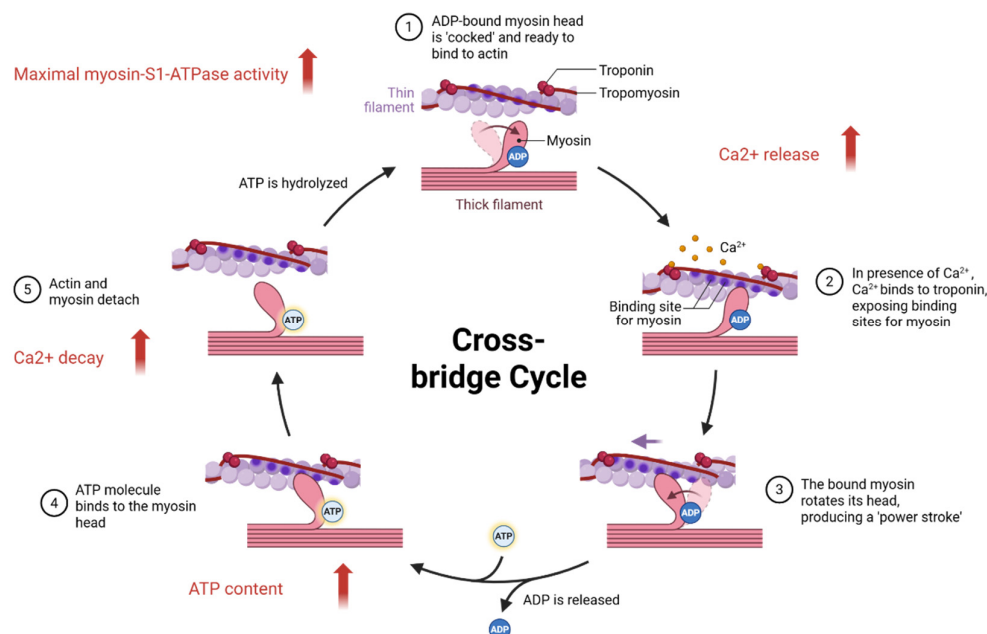
#### 2.4.2. More Cardiomyocyte Survival

Increased cardiomyocyte survival supports cardiac function, and *in vivo* mouse studies demonstrated that emergency EGCG administration during MI and MIRI significantly reduced cardiomyocyte mortality and improved cardiac function [78,79,95,96]. In *ex vivo* experiments using

the Langendorff isolated heart perfusion system (LIHPS) to maintain cardiac activity, supplementation of the perfusate with EGCG during the induction of MIRI [99,102] or CPB related injury [98] reduced cardiomyocyte apoptosis and mitigated cardiac dysfunction. Although one ex vivo MIRI study [100] reported no improvement in cardiac function, another study [101] employing the same methodology but altering the timing of EGCG administration demonstrated significant functional improvement. The negative findings of the former study may be attributable to suboptimal timing of administration, as EGCG was not delivered during the reperfusion period.

#### 2.4.3. Better Cardiomyocyte Function

EGCG reduced mitochondrial injury in MI and MIRI mice and prevented downregulation of  $\beta$ 1-adrenoceptors ( $\beta$ 1-ARs) on cardiomyocyte membranes in HF mice [92], both of which favor enhanced cardiomyocyte contractile function. However, the effects of EGCG on  $\beta$ 1-AR expression in cardiomyocyte membranes appear to be long-term, and whether it can elevate expression beyond baseline levels remains to be elucidated. The mechanisms underlying EGCG-mediated enhancement of cardiomyocyte contractile and diastolic function primarily involve regulation of mitochondrial activity, ion channel dynamics, and thin-filament function, with their mechanisms illustrated in **Figure 3**. Even in the absence of injurious stimuli, EGCG treatment increased mitochondrial activity in mouse CMs and improved cardiac function [89,97]. In vitro studies have demonstrated that EGCG augments calcium transient peaks in CMs [97,103], thereby enhancing cardiomyocyte contractility. In addition, EGCG directly interacts with cTn, suggesting therapeutic potential for patients with troponin mutations. EGCG modulates troponin calcium sensitivity, accelerates calcium dissociation from troponin, facilitates sarcomere relaxation [85,104,106], restores excitation–contraction coupling [105], and increases maximal myosin ATPase activity [106], thereby enhancing thin-filament contractile and diastolic function.



**Figure 3.** EGCG increases calcium transients, enhancing the number of activated cross-bridges during excitation-contraction coupling, while also increasing ATP content to provide potential energy for more myosin, thereby improving cardiomyocyte contractile function. In addition, EGCG increases ATPase activity, accelerating the detachment of myosin and actin, reduces the increased calcium sensitivity caused by troponin mutations, and accelerates the detachment of troponin from calcium ions, thereby improving the diastolic function of cardiomyocytes.

### 3. Adverse Reactions of Epigallocatechin Gallate

In preclinical toxicology studies, administration of EGCG at 50 mg/kg intravenously (iv, once daily) for 10 days or 2000 mg/kg orally (po, once daily) for 10 days did not induce genotoxicity in mice [107]. Similarly, oral EGCG at 500 mg/kg daily for 13 weeks did not cause dermal irritation in rats [108], and dietary supplementation with 1400, 4200, or 14,000 mg/kg EGCG during organogenesis was non-toxic to pregnant rats or their fetuses [109]. Oral EGCG reduces the bioavailability of iron [110], folic acid [111], and other drugs [112], by inhibiting their absorption. Moreover, although EGCG acts as an antioxidant, it exhibits pro-oxidative effects at higher doses [113,114]. In vitro, hepatocytes exhibited damage upon exposure to 200  $\mu$ M EGCG. In vivo, a single intraperitoneal injection of 100 mg/kg EGCG elevated plasma ALT levels in mice, and doses of 150 mg/kg caused death within 22 hours [115]. Cai et al. reported that oral EGCG at 500 or 1000 mg/kg daily for 8 days induced mild cardiac fibrosis in mice [116]. Similarly, Rasheed et al. observed that intraperitoneal EGCG at 100 mg/kg daily for 4 days caused mild myocardial injury in diabetic mice [117]. In LIHPS experiments, low-dose EGCG (20  $\mu$ M) enhanced cardiac contractility, whereas high-dose EGCG (50  $\mu$ M) increased the incidence of arrhythmia and diastolic dysfunction [118]. Overall, animal studies indicate that adverse effects of EGCG occur only at relatively high doses, far exceeding those required for therapeutic efficacy.

In clinical studies, the most frequently reported adverse effects are hepatotoxicity and gastrointestinal disturbances, particularly when consumed on an empty stomach [119,120]. A few case reports have suggested that EGCG may cause severe liver injury [121], however, given the very low incidence, current evidence is insufficient to establish a definitive causal relationship. In healthy volunteers, EGCG was shown to reduce folic acid bioavailability [122], although the doses and duration required to induce clinical folate deficiency remain unclear. A daily oral dose of 800 mg EGCG for 4 weeks was reported to be safe in healthy individuals [123]. According to the European Food Safety Authority, average daily intake of EGCG from GT ranges from 90 to 300 mg/day, reaching up to 866 mg/day in heavy tea drinkers [124]. Thus, EGCG intake through tea consumption is considered safe. Large-scale population studies have reported no association between tea consumption during pregnancy and adverse outcomes [125]. Subsequent clinical studies have shown that even higher oral doses of EGCG administered for 12 to 16 weeks (up to 865 mg/day) did not elicit significant adverse reactions, supporting its safety [23,30]. In a clinical trial, topical application of an EGCG spray (2574  $\mu$ mol/L) three times daily for 2 weeks to treat severe radiotherapy-induced dermatitis revealed no EGCG-related adverse reactions [126].

Overall, the threshold doses of EGCG that induce serious adverse effects vary substantially depending on the administration route, treatment duration, and comorbidities of the subjects. The degree of oxidative stress also differs between healthy individuals and patients with T2DM, MI, or MIRI. In populations with high oxidative stress, doses considered therapeutic may correspond to high doses in healthy individuals, potentially exacerbating oxidative stress and inducing adverse effects. Current clinical research primarily focuses on oral administration, typically at relatively low doses, while the safety profile of higher doses and alternative administration routes requires further investigation. Collectively, the available evidence indicates that EGCG is generally safe at dietary and clinically tested doses, but careful dose selection and population-specific evaluation remain essential for its therapeutic application.

### 4. Conclusions and Future Perspectives

As a natural antioxidant and anti-inflammatory agent, long-term EGCG treatment improves glucose and lipid metabolism, prevents CAD progression, and alleviates adverse cardiac remodeling associated with T2DM, MI, HF, and related conditions. In acute injuries such as MI and MIRI, emergency EGCG administration reduces cardiomyocyte injury and suppresses RCD. The cardioprotective effects of EGCG have been validated in numerous cellular and small-animal studies. However, research in large-animal and comorbidity models remains limited, and clinical trials have

primarily focused on metabolic outcomes, with few exploring EGCG in MI, MIRI, or CPB. Given its cardioprotective efficacy and favorable safety profile, further studies are warranted in large-animal models, comorbidity settings, and clinical trials assessing different EGCG dosages, administration routes, and timing strategies.

Particular attention should be paid to tailoring EGCG administration to disease-specific contexts. For instance, in the emergency management of MI and MIRI, intravenous administration is superior to oral delivery, as it circumvents the problem of low oral bioavailability, reduces the need for excessive oral dosing to achieve therapeutic concentrations, and minimizes the risk of adverse effects. By contrast, for chronic conditions such as T2DM, AS, and HF, oral administration is more practical, with dosing requirements—dependent on disease severity—differing substantially from those for intravenous therapy. In animal models, the safe oral dose may reach 500 mg/kg per day, whereas efficacy studies commonly employ ~50 mg/kg per day, equivalent to approximately 2500 mg/day in humans. Yet, the highest dose tested in current clinical trials does not exceed 1000 mg/day, and the safety and efficacy of higher oral doses remain to be clarified. For long-term oral administration, dividing the daily dose into three portions taken after meals is preferable, as this strategy reduces gastrointestinal irritation and minimizes fluctuations in plasma drug concentrations. Moreover, the timing of administration is critical. In MIRI, EGCG administration should precede reperfusion to counteract the surge of oxidative stress and inflammation during this phase.

Clinical investigations of EGCG can be extended to diverse clinical contexts. In designing dosing regimens, clinical applications should account for disease severity, the nature of injury (acute vs. chronic), and the practicality of administration. For example, to evaluate the preventive effect of EGCG on MINS, a relatively mild surgical complication, EGCG could be incorporated into the preoperative clear-liquid diet. To explore its therapeutic effect in MIRI, EGCG could be administered intravenously before or during reperfusion in patients with MI. For CPB, EGCG could be added to the cardioplegic solution to protect the arrested heart. In summary, dosing strategies for different administration routes must be carefully optimized, and the safety of these regimens should be rigorously monitored in human populations.

Moreover, EGCG could be applied as a coating for arterial stents in patients with AS [127], or incorporated into nanocomposite formulations with other therapeutic agents [128–130], offering further opportunities for drug-combination strategies. In addition to conducting more clinical studies, the combination of EGCG with other drugs through nanotechnology to design new multifunctional composite drugs is also an important research direction for future EGCG research.

## Abbreviations

The following abbreviations are used in this manuscript:

GT	Green tea
GTE	Green tea extract
EGCG	Epigallocatechin gallate
MS	Metabolic syndrome
T2DM	Type 2 diabetes mellitus
GDM	Gestational diabetes mellitus
DCM	Diabetic cardiomyopathy
ATTR-CM	Amyloidotic transthyretin cardiomyopathy
wtATTR-CM	wild-type transthyretin amyloid cardiomyopathy
AS	Atherosclerosis
CAD	Coronary artery disease
MI	Myocardial infarction
MIRI	Myocardial ischemia-reperfusion injury
MINS	Myocardial injury after non-cardiac surgery
RCM	Restrictive cardiomyopathy
HCM	Hypertrophic cardiomyopathy

HF	Heart failure
ApoE	Apolipoprotein E
SD	Sprague-Dawley
SHR	Spontaneously hypertensive rats
HUVECs	Human umbilical vein endothelial cells
HASMCs	Human aortic smooth muscle cells
MEFs	Mouse embryonic fibroblasts
CMs	Cardiomyocytes
CFs	Cardiac fibroblasts
TF	Thin filament
<i>P. gingivalis</i>	<i>Porphyromonas gingivalis</i>
NAM	Nicotinamide
STZ	Streptozotocin
ISO	Isoprenaline
AAC	Abdominal aortic constriction
TAC	Transverse aortic constriction
LADO	Left anterior descending artery occlusion
LMCAO	Left main coronary artery occlusion
LIHPS	Langendorff isolated heart perfusion system
CPB	Cardiopulmonary bypass
Ang II	Angiotensin II
P/I	Phorbol 12-myristate 13-acetate and ionomycin
$\beta$ -GP	$\beta$ -Glucopyranosyl phosphate
HRI	Hypoxia-reoxygenation injury
LA	Lipid abnormality
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
VLDL-C	Very low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
AIP	Atherogenic index of plasma
HOMA-IR	Homeostasis model assessment of insulin resistance
OGTT	Oral glucose tolerance test
FBG	Fasting blood glucose
HbA1C	Hemoglobin A1C
GLP-1	Glucagon-like peptide 1
ROS	Reactive oxygen species
SOD	Superoxide dismutase
Mn-SOD	Manganese superoxide dismutase
CAT	Catalase
GPX4	Glutathione peroxidase 4
GSH	Glutathione
VC	Vitamin C
VE	Vitamin E
CER	Ceruloplasmin
T-AOC	Total antioxidant capacity
MDA	Malondialdehyde
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
MPO	Myeloperoxidase
MCP-1	Monocyte chemoattractant protein-1
VEGFA	Vascular endothelial growth factor
ICAM-1	Intercellular adhesion molecule-1

VCAM-1	Vascular cell adhesion molecule-1
CTGF	Connective tissue growth factor
EMMPRIN	Extracellular matrix metalloproteinase inducer
MMPs	Matrix metalloproteinases
EndMT	Endothelial-to-mesenchymal transition
COL	Collagen
HW	Heart weight
BW	Body weight
TL	Tibia length
SIRT1	Silent information regulator 1
mtDNA	Mitochondrial DNA
SERCA2a	Sarcoplasmic reticulum Ca-ATPase
$\beta$ 1-AR	$\beta$ 1-adrenoceptors
cTn	Cardiac troponin
cTnC	Cardiac troponin C
cTnT	Cardiac troponin T
cTnI	Cardiac troponin I
CK	Creatine kinase
CK-MB	Creatine kinase-MB
LDH	Lactate dehydrogenase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ALT	Alanine transaminase
RCD	Regulated cell death
CO	Cardiac output
SAP	Systolic arterial pressure
MAP	Mean arterial pressure
DAP	Diastolic arterial pressure
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic dimension
LVESD	Left ventricular end-systolic dimension
LVSP	Left ventricular systolic pressure
LVEDP	Left ventricular end-diastolic pressure
LVDP	Left ventricular developed pressure
$\pm dp/dt$ max	Maximal left ventricular pressure variation rate
FS	Fractional shortening
TXA2	Thromboxane A2
ATG4C	Autophagy related 4C
HDAC	Histone deacetylase
KATP	ATP-sensitive potassium channels
NS	Not Significant

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