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REVIEW

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A review of cardioprotective effect of ginsenosides in chemotherapy-induced cardiotoxicity

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Abstract

Chemotherapy-induced cardiotoxicity is a significant concern in cancer treatment, as certain chemotherapeutic agents can have adverse effects on the cardiovascular system. This can lead to a range of cardiac complications, including heart failure, arrhythmias, myocardial dysfunction, pericardial complications, and vascular toxicity. Strategies to mitigate chemotherapy-induced cardiotoxicity may include the use of cardioprotective agents (e.g., dexrazoxane), dose adjustments, alternative treatment regimens, and the implementation of preventive measures, such as lifestyle modifications and the management of cardiovascular risk factors. Ginsenosides, the active compounds found in ginseng (*Panax ginseng*), have been studied for their potential cardioprotective effects in the context of chemotherapy-induced cardiotoxicity. In this review, we investigate the cardioprotective effect of ginsenosides in chemotherapy-induced cardiotoxicity. Ginsenosides have been shown to possess potent antioxidant properties, which can help mitigate the oxidative stress and inflammation associated with chemotherapy-induced cardiac injury. They can modulate the expression of antioxidant enzymes and reduce the production of reactive oxygen species, thereby protecting cardiomyocytes from damage. Ginsenosides can also inhibit apoptosis (programmed cell death) of cardiomyocytes, which is a key mechanism underlying chemotherapy-induced cardiotoxicity. Modulation of ion channels, improvement of lipid profiles, anti-platelet and anti-thrombotic effects, and promotion of angiogenesis and neovascularization are another important mechanisms behind potential effects of ginsenosides on cardiovascular health. Ginsenosides can improve various parameters of cardiac function, such as ejection fraction, fractional shortening, and cardiac output, in animal models of chemotherapy-induced cardiotoxicity. The cardioprotective effects of ginsenosides have been observed in preclinical studies using various chemotherapeutic agents, including doxorubicin, cisplatin, and 5-fluorouracil. However, more clinical studies are needed to fully elucidate the therapeutic potential of ginsenosides in preventing and managing chemotherapy-induced cardiotoxicity in cancer patients.

Keywords: Ginsenoside, Ginseng, Cardiotoxicity, Chemotherapy, Cardioprotective

Introduction

Chemotherapy-induced cardiotoxicity refers to damage to the heart caused by certain chemotherapy drugs [1]. This is a significant concern in cancer treatment, as it can lead to various cardiac complications, including heart failure, arrhythmias (abnormal heart rhythms), hypertension (high blood pressure), myocarditis (inflammation of the heart muscle), etc. [2]. The risk and severity of cardiotoxicity can depend on several factors, including the type of chemotherapy drug, dosage, duration of treatment, combination with other treatments, and the patient's overall health and pre-existing heart conditions [3]. There are several classes of chemotherapy drugs known to potentially cause cardiotoxicity, with varying mechanisms of action such as anthracyclines, alkylating agents, antimetabolites, monoclonal antibodies, tyrosine kinase inhibitors, and proteasome inhibitors [4–6]. The management of chemotherapy-induced cardiotoxicity involves a multidisciplinary approach, including oncologists, cardiologists, and other healthcare professionals. Strategies may include monitoring (regular heart function monitoring before, during, and after chemotherapy), dose adjustment (modifying the dose or schedule of the chemotherapy drug), medication (such as ACE inhibitors, beta-blockers, or dexrazoxane), lifestyle changes (encouraging a healthy lifestyle, including a balanced diet, regular exercise, and avoiding tobacco and excessive alcohol) [7–9]. Ginseng, a traditional herbal remedy used for centuries in East Asia and North America, has been investigated for its potential cardioprotective effects [10]. It contains several active components, including ginsenosides, which are believed to be responsible for most of its health benefits [11]. Ginsenosides are the primary active compounds found in ginseng (Panax ginseng), a widely used medicinal herb with a long history of traditional use in Asian countries. Ginsenosides are a diverse group of triterpene saponins that have been extensively studied for their various pharmacological properties, including their potential therapeutic applications in cardiovascular diseases [12–14]. In this review article, we assessed the cardioprotective effect of ginsenosides in chemotherapy-induced cardiotoxicity.

Chemotherapy-induced cardiotoxicity

Chemotherapy-induced cardiotoxicity refers to the adverse effects of chemotherapy drugs on the function and structure of the heart (Table 1). Mechanisms of chemotherapy-induced cardiotoxicity are summarized in Fig. 1. These effects can lead to a decline in cardiac performance and even heart failure in some cases. Cardiotoxicity is a concerning side effect of certain chemotherapeutic agents and can significantly impact a patient's quality of life and survival [2].

The specific types of cardiotoxicity and their characteristics include (Fig. 2):

1. Cardiomyopathy: this is the most common form of cardiotoxicity, characterized by a decrease in cardiac function, particularly left ventricular systolic function. It can lead to heart failure and is often associated with anthracyclines, a common class of chemotherapeutic drugs [15].

Table 1 Some key points about chemotherapy-induced cardiotoxicity

Aspect	Information
Definition	Damage to the heart muscle caused by certain chemotherapy drugs
Mechanism	Interference with cardiac cell function, leading to heart dysfunction
Risk factors	Pre-existing heart conditions, high doses of chemotherapy, certain drugs
Common Chemotherapies	Doxorubicin, trastuzumab, fluorouracil, paclitaxel
Types of cardiotoxicity	Acute (within days to weeks), chronic (months to years), delayed
Symptoms	Shortness of breath, chest pain, fatigue, swelling in legs
Monitoring	Echocardiograms, EKGs, biomarkers like troponin and BNP
Management	Cardioprotective medications, monitoring heart function, lifestyle changes
Prevention	Limiting cumulative doses, cardioprotective drugs, monitoring heart function
Prognosis	Varies depending on drug, dose, patient factors

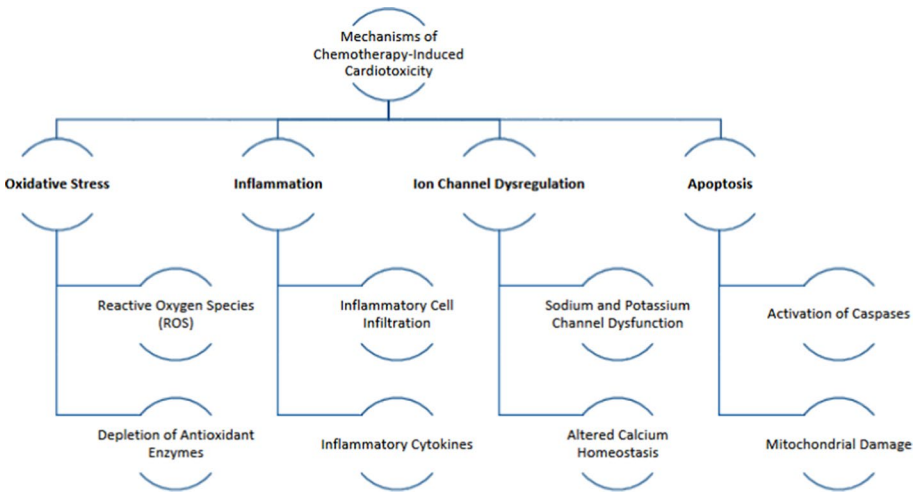

Fig. 1 Mechanisms of chemotherapy-induced cardiotoxicity

2. Arrhythmias: chemotherapy can disrupt the electrical conduction system of the heart, leading to abnormal heart rhythms. These arrhythmias can be life-threatening and require immediate medical attention [16].
3. Myocardial ischemia and infarction: some chemotherapy drugs can damage the blood vessels supplying the heart, leading to reduced blood flow and oxygen supply to the heart muscle, resulting in ischemia or myocardial infarction (heart attack) [17].
4. Pericardial disease: chemotherapy can cause inflammation or fluid accumulation in the pericardium, the sac surrounding the heart [18]. This can lead to pericarditis or pericardial effusion, causing chest pain and potentially impacting heart function [19].
5. Vascular toxicity: chemotherapy may damage blood vessels, leading to endothelial dysfunction and vascular disorders such as Raynaud's phenomenon or peripheral vascular disease [20].
6. Cardiac autonomic neuropathy: some chemotherapeutic agents can damage the nerves supplying the heart, leading to abnormal heart rate and blood pressure control [7, 21, 22].

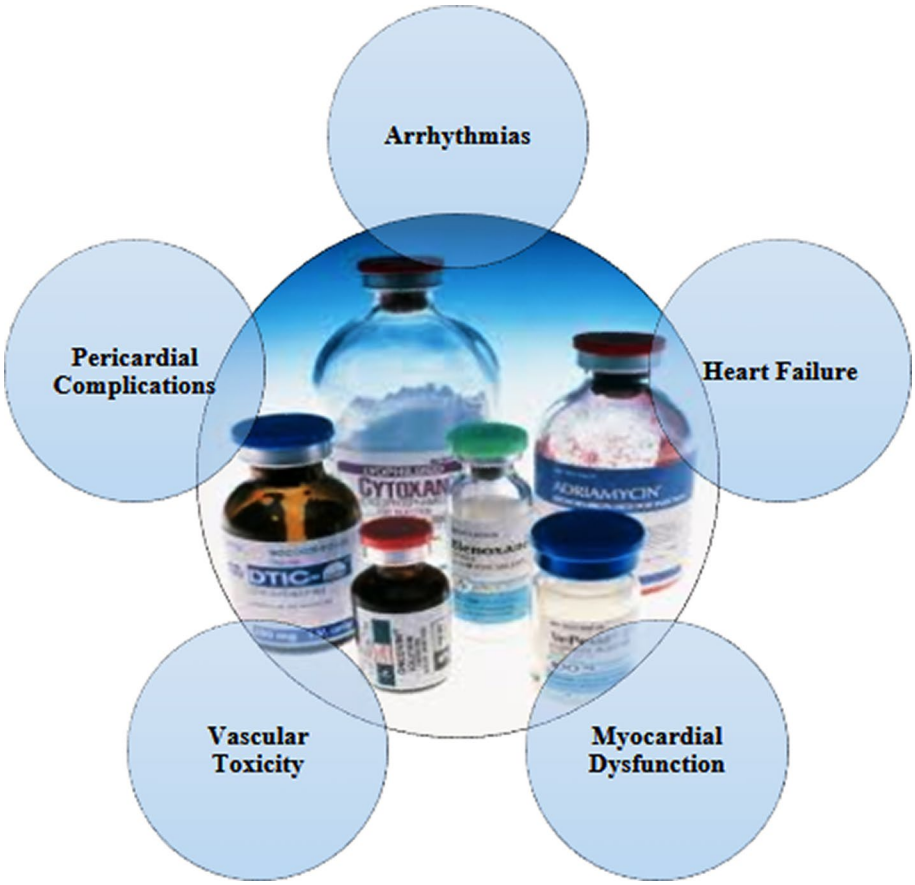

Fig. 2 Overview of chemotherapy-induced cardiotoxicity

The risk factors for developing chemotherapy-induced cardiotoxicity include:

- Type and dose of chemotherapy: certain chemotherapeutic agents, such as anthracyclines and trastuzumab, are more cardiotoxic than others (Table 2). Higher cumulative doses and longer duration of treatment also increase the risk.
- Previous cardiac disease: patients with pre-existing heart conditions or risk factors, such as hypertension or diabetes, are more susceptible to cardiotoxicity from chemotherapy.
- Age: older patients tend to have a higher risk of cardiotoxicity, possibly due to age-related changes in cardiac function and decreased cardiac reserve [23].
- Radiation therapy: combined radiation therapy to the chest area can further increase the risk of cardiotoxicity [24].
- Genetic predisposition: certain genetic variations may influence an individual's susceptibility to cardiotoxicity [1, 15, 25].

Management and prevention strategies for chemotherapy-induced cardiotoxicity include:

Table 2 List of the most important chemotherapy drugs with cardiotoxicity

Chemotherapy agent	Mechanism of cardiotoxicity	Risk factors	Monitoring recommendations
Anthracyclines (e.g., doxorubicin, epirubicin)	- Generation of free radicals leading to oxidative stress - Interference with topoisomerase II-β leading to DNA damage	- Cumulative dose - Prior cardiac disease - Older age - Radiation therapy	- Baseline and periodic echocardiography or MUGA scans - Cardiac biomarkers (troponin, BNP)
Trastuzumab	- Inhibition of HER2 signaling in cardiomyocytes	- Prior anthracycline exposure - Older age - Hypertension	- Baseline and periodic echocardiography or MUGA scans
Tyrosine kinase Inhibitors (e.g., sunitinib, sorafenib)	- Inhibition of VEGF signaling - Hypertension	- Underlying cardiovascular disease	- Baseline and periodic monitoring of blood pressure, ECG, echocardiography
Alkylating agents (e.g., cyclophosphamide)	- Myocardial injury and fibrosis	- High-dose regimens	- Baseline and periodic monitoring of cardiac function
Proteasome inhibitors (e.g., bortezomib)	- Mitochondrial dysfunction - Oxidative stress	- Underlying cardiovascular disease	- Baseline and periodic monitoring of cardiac function

- Cardiac monitoring: regular cardiac assessments, including echocardiograms and electrocardiograms, are crucial for early detection of cardiotoxicity. Close monitoring allows for prompt intervention and adjustment of chemotherapy regimens if necessary [26].
- Cardioprotective medications: medications such as angiotensin-converting enzyme (ACE) inhibitors or beta-blockers may be prescribed to protect the heart and improve cardiac function [27, 28].
- Adjustments to chemotherapy: in some cases, reducing the dose or changing the chemotherapy regimen may be necessary to minimize cardiotoxic effects [21].
- Cardiac rehabilitation: cardiac rehabilitation programs can help improve cardiovascular health and reduce the impact of cardiotoxicity through supervised exercise, education, and lifestyle modifications [29, 30].
- Risk factor management: controlling cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, is essential to minimize the overall cardiac risk in patients undergoing chemotherapy [31–33].

Ginsenosides

Ginsenosides are the primary active compounds found in ginseng, a plant that has been widely used in traditional Chinese medicine for thousands of years. Ginseng comes in various species, such as Panax ginseng (Korean or Asian ginseng), Panax quinquefolius (American ginseng), and Panax notoginseng, each containing different

profiles and concentrations of ginsenosides. These compounds are believed to be responsible for the plant's medicinal properties [34, 35].

Structure and classification

Ginsenosides are classified as triterpenoid saponins, which means they are glycosides (molecules where a sugar part is bound to a non-sugar part) of triterpene derivatives. The structure of ginsenosides consists of a steroidal-like backbone attached to one or more sugar moieties. The variation in the number and position of the sugar moieties, as well as the structure of the aglycone (non-sugar) part, accounts for the diversity of ginsenosides [36]. The main types of ginsenosides are summarized in Table 3. Ginsenosides are also commonly classified into two main groups based on the aglycone structure:

- Rb group (including Rb1, Rb2, Rb3, etc.): characterized by a dammarane-type structure with a 20(S)-protopanaxadiol group.
- Rg group (including Rg1, Rg2, Rg3, etc.): characterized by a dammarane-type structure with a 20(S)-protopanaxatriol group.

There are more than 150 identified ginsenosides, and ongoing research continues to discover new variants and investigate their unique effects [36–38].

Biological effects and potential health benefits

Ginsenosides are thought to underlie most of the therapeutic properties attributed to ginseng, including:

- Anti-inflammatory effects: they can modulate the immune system by reducing the production of pro-inflammatory cytokines [39].
- Antioxidant properties: ginsenosides can help reduce oxidative stress by neutralizing free radicals and enhancing the body's own antioxidant defenses [40].
- Cardiovascular health: they may offer cardioprotective effects by improving blood circulation, reducing blood pressure, and possessing anti-platelet activities [41].

Table 3 Classification of ginsenoside, structure, and example

Ginsenoside type	Structure	Examples
Protopanaxadiol (PPD)	- Dammarane-type triterpene structure - Two sugar moieties attached	- Rb1 - Rb2 -Rc - Rd
Protopanaxatriol (PPT)	- Dammarane-type triterpene structure - One sugar moiety attached	- Re - Rf - Rg1
Oleanane-type	- Oleanane-type triterpene structure - One or two sugar moieties attached	- Ro
Ocotillol-type	- Ocotillol-type triterpene structure - One sugar moiety attached	- F11 - F12
Floralginsenoside	- Dammarane-type triterpene structure - Ester-linked fatty acid moiety	- Rg6 - Rk3 - Rh4

- Neuroprotective effects: some ginsenosides can provide protection against neurodegenerative diseases by promoting neural growth, reducing amyloid-beta peptide toxicity in Alzheimer's disease, and exhibiting anti-apoptotic properties [42].
- Anti-cancer properties: ginsenosides may inhibit tumor growth through various mechanisms, including inducing apoptosis in cancer cells, inhibiting angiogenesis (formation of new blood vessels that feed tumors), and modulating pathways involved in cancer cell proliferation.
- Improving mental performance and mood: ginsenosides can enhance cognitive function and may help in the treatment of depression and anxiety [43, 44].

Considerations and interactions

While ginsenosides offer various health benefits, their effects can differ significantly depending on the specific ginsenoside, its concentration, and the individual's unique health profile. Moreover, ginseng and ginsenosides can interact with certain medications, including blood thinners, diabetes medications, and drugs metabolized by certain liver enzymes. Therefore, it is important for individuals to consult with healthcare providers before starting any ginseng supplement, especially if they have pre-existing health conditions or are taking other medications [40, 45].

Cardioprotective effect of ginsenosides

Ginsenosides, have been extensively studied for their cardioprotective effects (Fig. 3). These natural compounds exert a variety of actions on the cardiovascular system, offering potential benefits in the prevention and treatment of heart diseases [46]. The cardioprotective effects of ginsenosides are attributed to several mechanisms, including antioxidant activity, anti-inflammatory effects, modulation of ion channels and blood pressure, improvement in lipid profiles, and protection against myocardial ischemia–reperfusion injury. Various mechanisms were proposed for cardioprotective effect of ginsenosides [47, 48]. We reviewed the main proposed mechanisms for cardioprotective effect of ginsenosides.

Antioxidant activity

The antioxidant activity of ginsenosides plays a significant role in their cardioprotective effects [40]. Oxidative stress, which involves the production of reactive oxygen species (ROS) exceeding the body's antioxidant defense capacity, is a key factor in the development and progression of cardiovascular diseases. It contributes to endothelial dysfunction, inflammation, atherosclerosis, hypertension, and myocardial infarction. Ginsenosides have strong antioxidant properties, helping to neutralize harmful free radicals and reduce oxidative stress, a key factor in the development of cardiovascular diseases [49, 50]. By combating oxidative stress, ginsenosides can protect the heart and blood vessels from damage. Ginsenosides have demonstrated potent antioxidant properties that can mitigate oxidative stress and thereby offer protection against various heart conditions. Ginsenosides can directly scavenge free radicals and reactive oxygen species, reducing oxidative damage to cellular components such as lipids, proteins, and DNA. This protective effect helps maintain the integrity and function of cardiac cells and blood

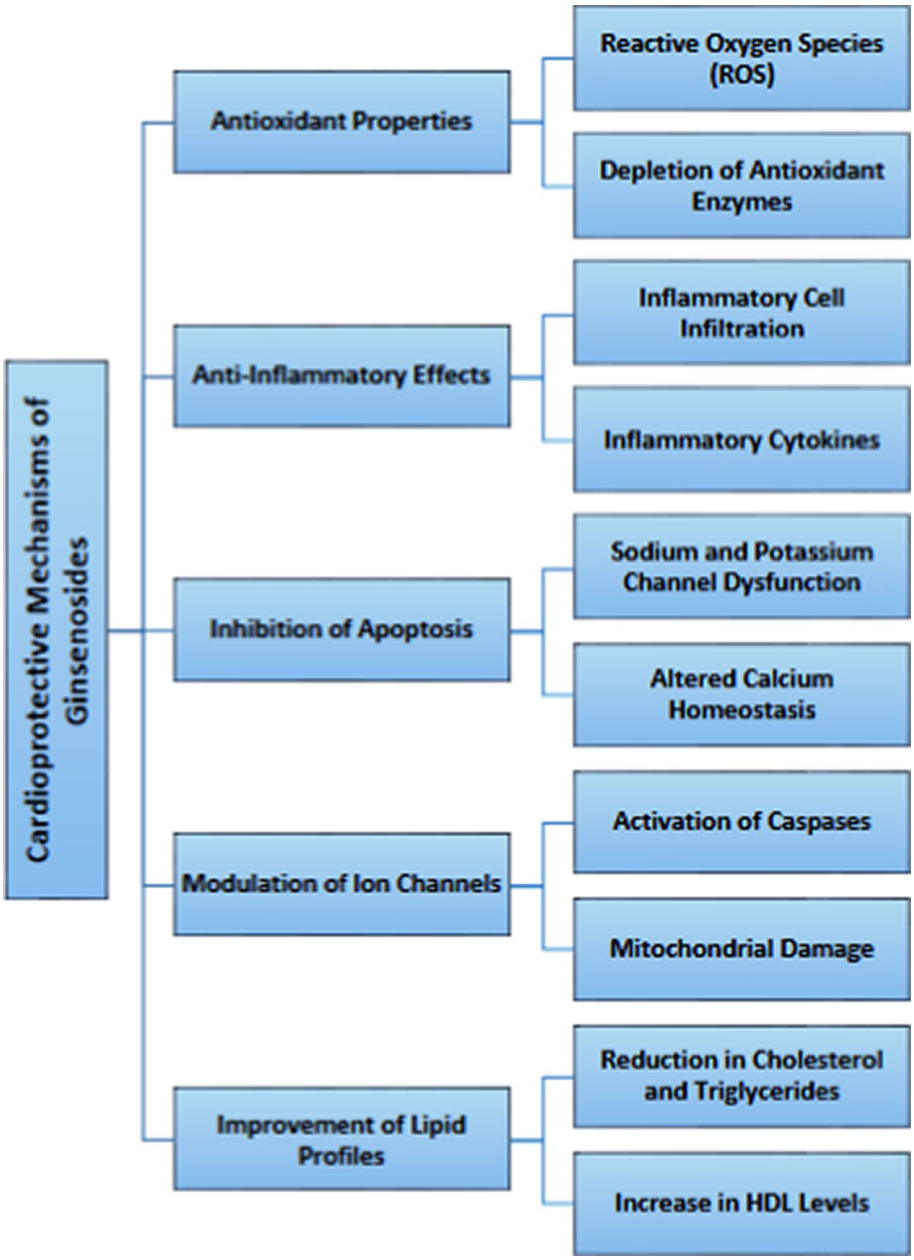

Fig. 3 Cardioprotective mechanisms of ginsenosides

vessels [51]. Ginsenosides can also upregulate the expression of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [52]. By boosting the body's own antioxidant defense mechanisms, ginsenosides help to neutralize ROS more effectively and maintain redox balance. Oxidative stress can activate inflammatory pathways, contributing to the development of atherosclerosis and other cardiovascular disorders. Ginsenosides have been shown to inhibit the production of pro-inflammatory cytokines and adhesion molecules, partly by modulating signaling pathways such as NF-κB, which are activated by oxidative stress. This

anti-inflammatory action complements the direct antioxidant effects of ginsenosides and contributes to their overall cardioprotective benefits [53, 54].

Endothelial dysfunction is an early marker of cardiovascular disease and involves reduced bioavailability of nitric oxide (NO) and impaired vasodilation. Oxidative stress plays a critical role in endothelial dysfunction [55]. Ginsenosides can enhance endothelial function by reducing oxidative damage and improving NO bioavailability, leading to better vasodilation and blood flow. Atherosclerosis, characterized by the accumulation of lipids and fibrous elements in the large arteries, is a major risk factor for cardiovascular diseases. Oxidative modification of LDL cholesterol is a key step in the development of atherosclerosis. Ginsenosides, through their antioxidant activity, can prevent the oxidative modification of LDL, thus reducing the formation of atherosclerotic plaques [56, 57].

Anti-inflammatory effects

Inflammation is a key underlying mechanism in the development and progression of cardiovascular diseases, including atherosclerosis, myocardial infarction, and hypertension [58]. By modulating the body's inflammatory response, ginsenosides can help mitigate the risk and severity of these conditions. Chronic inflammation contributes to the progression of cardiovascular diseases. Ginsenosides can modulate the immune response and reduce inflammation, thereby offering protection against vascular inflammation and atherosclerosis (the buildup of plaque in the arteries) [57]. The anti-inflammatory effects of ginsenosides contribute significantly to their cardioprotective properties. Ginsenosides have been shown to suppress the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) [59, 60]. These cytokines play significant roles in the inflammatory process associated with cardiovascular diseases. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway is a critical regulator of inflammation. Ginsenosides can inhibit the activation of the NF-κB pathway, thereby reducing the expression of genes involved in inflammation and immune responses [39]. Endothelial dysfunction, a precursor to atherosclerosis, involves the increased expression of adhesion molecules that facilitate the attachment and migration of inflammatory cells into the vessel wall [55]. Ginsenosides can reduce the expression of these adhesion molecules, decreasing the infiltration of monocytes/macrophages and the development of atherosclerotic lesions. Ginsenosides can modulate the activity of various immune cells, including macrophages, lymphocytes, and dendritic cells [61]. By influencing the behavior of these cells, ginsenosides can help shift the immune response from a pro-inflammatory state to a more balanced or anti-inflammatory state. By reducing inflammation, ginsenosides can help prevent the initiation and progression of atherosclerosis, a major cause of heart attacks and strokes [57]. Post-myocardial infarction, inflammation plays a crucial role in tissue damage and repair [62]. Ginsenosides can potentially reduce excessive inflammatory responses, promoting better healing and reducing the risk of heart failure. Inflammation contributes to the development of hypertension. The anti-inflammatory effects of ginsenosides may help in managing blood pressure levels, thereby offering protection against hypertension-related cardiac damage [63, 64].

Modulation of ion channels and blood pressure

Certain ginsenosides influence the activity of ion channels in heart cells, which can help regulate heart rhythm and prevent arrhythmias. Additionally, some studies have shown that ginsenosides can help lower high blood pressure, a major risk factor for heart disease, by improving vascular relaxation and reducing arterial stiffness. Ginsenosides have shown promising potential in modulating ion channels and regulating blood pressure, which are critical aspects of cardioprotection. Ion channels, including calcium (Ca^{2+}), potassium (K^{+}), and sodium (Na^{+}) channels, play vital roles in maintaining cardiac function and vascular tone [65]. Dysregulation of these channels can lead to various cardiovascular diseases, including hypertension, arrhythmias, and heart failure. Ginsenosides can exert protective effects on the heart and blood vessels through their interaction with these ion channels and their impact on blood pressure regulation. Ginsenosides can modulate calcium channels in cardiac and smooth muscle cells [45, 66]. By inhibiting L-type Ca^{2+} channels, ginsenosides can reduce Ca^{2+} influx, which leads to vasodilation and decreased cardiac contractility. This can help lower blood pressure and reduce the workload on the heart [67]. Activation of K^{+} channels in vascular smooth muscle cells by ginsenosides can lead to hyperpolarization and relaxation of these cells, contributing to vasodilation and blood pressure reduction. Additionally, modulation of K^{+} channels in cardiac cells can influence heart rate and protect against arrhythmias [43].

Although less studied, there is evidence that ginsenosides can also affect Na^{+} channels, potentially contributing to their cardiovascular effects. Ginsenosides have been observed to exert antihypertensive effects through multiple mechanisms, including direct vasodilation mediated by ion channel modulation and indirect effects such as antioxidative and anti-inflammatory actions. By promoting vasodilation and improving endothelial function, ginsenosides can help lower blood pressure. This is of particular importance in the prevention and management of hypertension, a major risk factor for cardiovascular diseases. The cardioprotective effects of ginsenosides related to ion channel modulation and blood pressure regulation include prevention of hypertension, protection against arrhythmias, maintain the electrical stability of cardiac cells, and reduction of cardiac workload [47, 63, 68].

Improvement in lipid profiles

Ginsenosides may also positively impact lipid metabolism, leading to reduced levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, while increasing high-density lipoprotein (HDL) cholesterol. A healthier lipid profile is associated with a lower risk of coronary heart disease. Ginsenosides have been associated with improvements in lipid profiles, which is an important aspect of cardioprotection. Dyslipidemia, characterized by elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and decreased high-density lipoprotein cholesterol (HDL-C), is a well-established risk factor for cardiovascular disease (CVD). By influencing lipid metabolism, ginsenosides can help mitigate this risk, contributing to the prevention and management of CVD [56, 69].

Ginsenosides can influence the absorption of lipids from the diet and modulate the biosynthesis of cholesterol in the liver [56]. For instance, certain ginsenosides may inhibit the activity of enzymes involved in cholesterol synthesis, such as HMG-CoA

reductase, leading to reduced levels of cholesterol. Ginsenosides may enhance the excretion of cholesterol by converting it to bile acids and promoting its elimination, thereby reducing circulating cholesterol levels. By increasing the expression of LDL receptors on hepatocytes, ginsenosides can enhance the clearance of LDL-C from the bloodstream, effectively lowering LDL-C levels. Ginsenosides have been reported to activate LPL, an enzyme that plays a crucial role in the hydrolysis of triglycerides in lipoproteins. This activity can lead to a decrease in triglyceride levels and an increase in HDL-C levels [70, 71]. The improvement in lipid profiles by ginsenosides contributes to cardioprotection in several ways:

- Reduction in atherosclerosis risk: lower levels of LDL-C and triglycerides, along with higher levels of HDL-C, can reduce the risk of atherosclerosis, a major cause of coronary artery disease, heart attacks, and strokes [57].
- Prevention of plaque formation: by decreasing the concentration of atherogenic lipoproteins in the blood, ginsenosides can help prevent the initiation and progression of plaque formation in the arteries [57].
- Improvement in endothelial function: a healthier lipid profile, particularly higher HDL-C levels, is associated with improved endothelial function, which is crucial for vascular health and the prevention of CVD [47, 72].

Protection against myocardial ischemia–reperfusion injury

Myocardial ischemia–reperfusion injury occurs when blood supply returns to the heart after a period of ischemia (lack of oxygen) and can cause significant damage to heart tissue. Ginsenosides have been shown to provide protection against this kind of injury by reducing cell death and improving heart function post-reperfusion [73].

Myocardial ischemia–reperfusion injury occurs when blood supply to the heart is restored after a period of ischemia (lack of blood flow). While reperfusion is necessary to salvage the ischemic myocardium, the sudden return of blood to the previously deprived tissues can paradoxically cause additional damage through oxidative stress, calcium overload, inflammation, and endothelial dysfunction. Ginsenosides have demonstrated potential in protecting against myocardial ischemia–reperfusion injury, thereby contributing to cardioprotection. Ginsenosides exert potent antioxidant effects, reducing oxidative stress by scavenging free radicals and enhancing the body's antioxidant defense system [74, 75]. This is particularly important in the context of ischemia–reperfusion injury, where the generation of reactive oxygen species (ROS) upon reperfusion plays a pivotal role in myocardial damage [76]. By mitigating oxidative stress, ginsenosides can help minimize the cell injury and apoptosis triggered by ROS. Inflammation is a hallmark of ischemia–reperfusion injury, contributing significantly to the extent of myocardial damage [75]. Ginsenosides have been shown to inhibit the activation of pro-inflammatory pathways and reduce the infiltration of inflammatory cells into the ischemic myocardium. By modulating the inflammatory response, ginsenosides can alleviate the extent of injury and promote a more favorable healing environment. Calcium overload is another critical factor in the pathogenesis of myocardial ischemia–reperfusion injury [77]. Ginsenosides can modulate the activity of ion channels, including

calcium and potassium channels, helping to stabilize intracellular calcium levels and prevent calcium-induced cellular injury during reperfusion. Endothelial dysfunction contributes to the impaired vasodilation and microvascular obstruction observed in myocardial ischemia–reperfusion injury. Ginsenosides can improve endothelial function, promoting vasodilation and thereby improving blood flow to the ischemic regions. This effect can help mitigate the no-reflow phenomenon, in which blood flow fails to adequately return to the ischemic tissues after reperfusion [78]. Ginsenosides have been shown to possess anti-apoptotic properties, protecting cardiac cells from programmed cell death triggered by ischemia–reperfusion injury. This is achieved through the regulation of apoptotic signaling pathways, including the inhibition of pro-apoptotic proteins and the activation of survival signaling cascades. Several studies have reported that ginsenosides can reduce the size of myocardial infarction (area of dead tissue) induced by ischemia–reperfusion injury. This effect is likely a cumulative result of their antioxidative, anti-inflammatory, ion-modulating, and anti-apoptotic actions [75, 79, 80].

Anti-platelet and anti-thrombotic effects

Ginsenosides can also prevent blood clots by inhibiting platelet aggregation and having anti-thrombotic properties, further contributing to their cardioprotective effects. Ginsenosides have shown promising anti-platelet and anti-thrombotic effects, contributing to their cardioprotective properties. Platelet aggregation and thrombosis (blood clot formation) play pivotal roles in the development of cardiovascular diseases, such as myocardial infarction (heart attack) and stroke. By inhibiting platelet aggregation and preventing thrombus formation, ginsenosides can help reduce the risk of these cardiovascular events [81, 82].

Ginsenosides can inhibit platelet aggregation, a crucial step in thrombus (blood clot) formation. Platelet aggregation is a complex process involving various signaling pathways, including the activation of platelet receptors and the subsequent rise in intracellular calcium levels, leading to platelet activation and aggregation [83]. Ginsenosides have been reported to interfere with the activation of platelets by various agonists, such as adenosine diphosphate (ADP) and collagen. This effect can be attributed to the modulation of signaling pathways involved in platelet activation [81]. Some ginsenosides can inhibit the mobilization of calcium within platelets, a crucial step for platelet activation and aggregation. By preventing calcium release, ginsenosides can reduce platelet aggregation. Ginsenosides may also affect the initial step of platelet adhesion to the vascular endothelium, further contributing to their anti-platelet action [47, 84].

The anti-thrombotic effects of ginsenosides are closely related to their anti-platelet activity, but also involve additional mechanisms that inhibit the overall process of thrombus formation:

- Enhancement of fibrinolysis: fibrinolysis is the process of breaking down blood clots, and ginsenosides have been suggested to enhance this process. By promoting the breakdown of fibrin, the primary component of blood clots, ginsenosides can help prevent the development of thrombosis [85].

– Inhibition of coagulation factors: preliminary research indicates that ginsenosides may also influence the coagulation cascade, which is responsible for the formation of blood clots. By modulating the activity of certain coagulation factors, ginsenosides could contribute to reduced clot formation [86–88].

Angiogenesis and neovascularization

The formation of new blood vessels can have beneficial impacts on cardiovascular health in certain situations, especially in chemotherapy-induced cardiotoxicity [89]. Ginsenosides like Rb1 and Rg1 can stimulate the growth of new blood vessels, a process known as angiogenesis, which might improve cardiovascular health by enhancing blood supply to the heart and promoting tissue repair after cardiac damage. Angiogenesis, the formation of new blood vessels from pre-existing ones, and neovascularization, which refers more broadly to the formation of functional blood vessels, are essential mechanisms for restoring blood supply to ischemic (blood flow-restricted) tissues, such as those affected by myocardial infarction (heart attack) or peripheral artery disease. Ginsenosides can stimulate the expression of angiogenic growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiopoietin [90, 91]. These factors play critical roles in initiating and promoting the angiogenic process by stimulating the proliferation, migration, and differentiation of endothelial cells, which form the lining of new blood vessels. Ginsenosides have been found to activate several intracellular signaling pathways that are involved in angiogenesis, including the PI3K/Akt and MAPK/ERK pathways [92, 93]. Activation of these pathways leads to endothelial cell survival, proliferation, and migration, all of which are essential for the formation of new blood vessels. By improving endothelial cell function, ginsenosides contribute to the formation of stable and functional blood vessels. This includes effects on endothelial cell adhesion, organization into tubular structures (a key step in vessel formation), and the release of factors that recruit supporting cells, such as smooth muscle cells, to stabilize the newly formed vessels [94–96].

Treatment outcomes by ginsenosides

Cardioprotective effects of ginsenosides against chemotherapy-induced cardiotoxicity are summarized in Table 4. This table summarizes the cardioprotective effects of various ginsenosides against chemotherapy-induced cardiotoxicity in different study models, including in vivo and in vitro experiments. The results demonstrate that ginsenosides can reduce cardiac damage markers, inflammation, and oxidative stress, while improving cell viability, antioxidant defenses, and mitochondrial function. Additionally, ginsenosides can inhibit apoptosis, autophagy, and fibrosis, and regulate cell survival pathways, including the PI3K/Akt pathway. These findings suggest that ginsenosides may be useful adjunct therapies to reduce the cardiotoxic effects of chemotherapy and improve treatment outcomes in cancer patients.

Table 4 Cardioprotective effects of ginsenosides against chemotherapy-induced cardiotoxicity

Study model	Chemotherapy drug (dosage)	Type of ginsenoside	Route of administration	Outcome	Refs.
In vivo/mice	Doxorubicin (20 mg/kg)	Ginsenoside Rb1 (20 mg/kg)	Oral	Improved survival rate and body weight in doxorubicin-treated mice Attenuated cardiac dysfunction, myocardium hypertrophy, and interstitial fibrosis Reduced oxidative stress and cardiomyocyte mitochondrion injury Mechanism of action: suppression of autophagy and ferroptosis	[97]
In vitro/H9C2 cells	Doxorubicin (1–5 μM/L)	Ginsenoside Rb1 (50, 100, 200, 400 μM)	Oral	Reduced cardiac damage markers: CK, CK-MB, cTnT, LDH, and MPO Increased antioxidant defenses: SOD, GSH, and decreased MDA Anti-inflammatory effects: decreased TNF-α, IL-1β, COX-2, and iNOS Anti-apoptotic effects: decreased Bax, Bad, Caspase-3, Caspase-8, and Caspase-9, and increased Bcl-2 Improved cell viability and reduced DNA fragmentation Inhibited expression of CYP1A1, CYP1A2, and AhR genes Activated PI3K/Akt pathway and inhibited GSK-3β	[98]
In vivo/rat	Doxorubicin (20 mg/kg)	Ginsenoside Rg3 (10 mg/kg)	Oral		

Table 4 (continued)

Study model	Chemotherapy drug (dosage)	Type of ginsenoside	Route of administration	Outcome	Refs.
In vivo/mice	Doxorubicin (3 mg/kg)	20(S)-ginsenoside Rh2 (Rh2) (5, 10, 20 mg/kg)	Intragastric	Reduced cardiac damage markers: LDH, CK, and CK-MB Downregulated expression of cardiac stress genes: a-SKA and b-MHC Anti-apoptotic effects: decreased mRNA expression of Bax, Caspase 3, and Caspase 9 Reduced oxidative stress: decreased ROS and Ca2 + overload Improved mitochondrial function: increased ATP production, MMR capacity, and decreased mtDNA Reduced mitochondrial damage: decreased mitochondrial membrane depolarization Increased Caspase 3/7 activity, suggesting a potential role in regulating apoptosis	

Table 4 (continued)

Study model	Chemotherapy drug (dosage)	Type of ginsenoside	Route of administration	Outcome	Refs.
In vivo/mice	Doxorubicin (6 mg/kg)	Ginsenoside Rg1 (50 mg/kg)	Intragastric	Reduced cardiac structural damage: decreased myofibrillar degeneration and disruption, and cardiac fibrosis Inhibited autophagy: suppressed conversion of LC3A to LC3B, and decreased expressions of ATG5 and sequestosome 1 (P62) Reduced endoplasmic reticulum (ER) stress: decreased ER dilation, and cleaved ATF6 and IRE1 protein expression Activated unfolded protein response (UPR): increased expressions of spliced X-box binding protein 1 (XBP1s) and GRP78 (ER chaperone) Regulated glutamine metabolism: increased glutamine fructose-6-phosphate amidotransferase (GFAT1) Inhibited cell growth and proliferation: decreased TIF1, mRNA translation, and phosphorylated ribosomal protein S6 kinase beta-1 (p-P70S6K)	[99]
In vivo/mice	Doxorubicin (15 mg/kg)	Ginsenoside Rg (180 mg/kg)	Oral	Reduced cardiac damage markers: LDH and CK-MB Decreased inflammation and fibrosis in the heart Inhibited apoptosis: decreased Cyt. C and cleaved caspase-3 Activated cell survival pathways: increased phosphorylation of Akt and Erk, and increased Bcl-2 and Bax ratio	[100]

Table 4 (continued)

Study model	Chemotherapy drug (dosage)	Type of ginsenoside	Route of administration	Outcome	Refs.
In vitro/H9C2 cells	Doxorubicin (2.5, 5, 10, 15, 20 μM)	Ginsenoside Rg2 (100, 200, 250, 300, 350, 400 μM)	Oral	Increased cell viability and decreased apoptotic rate in H9C2 cells Reduced oxidative stress: decreased ROS Activated cell survival pathways: increased p-Akt/Akt ratio and upregulated Akt phosphorylation Inhibited p53 expression, but not p-p53	[101]
In vitro/H9C2 cells	Adriamycin (2.67 μmol/L)	Ginsenoside Rb1 (0, 25, 50, 100, 200 μM)	Oral	Promoted cell proliferation and survival: ameliorated proliferation of injured cells, increased Ki67 and PCNA Reduced inflammation: decreased inflammatory cytokines, IL-1β, IL-6, and TNF-α Inhibited apoptosis: decreased p53, Bax, and cleaved-caspase3, and increased Bcl-2 Activated cell survival pathways: increased p-PI3K and p-AKT Regulated miRNA expression: increased expression of miR-130b Inhibited PTEN, a negative regulator of cell survival pathways	[102]

Table 4 (continued)

Study model	Chemotherapy drug (dosage)	Type of ginsenoside	Route of administration	Outcome	Refs.
In vivo/mice	Doxorubicin (2 mg/kg)	Ginsenoside Rh2 (20, 30 mg/kg)	Injected every other day	Reduced cardiac tissue damage: decreased cardiac histopathological changes Inhibited cell death: decreased apoptosis and necrosis Prevented fibrosis: decreased fibroblast to myofibroblast transition and endothelial-mesenchymal transition Inhibited inflammation: decreased expression of IL-1β, TNF-α, and IL-6 Reduced Toll-like receptor (TLR) expression: decreased TLR2, TLR6, TLR7, TLR8, TLR11, and TLR13 Inhibited TGF-β signaling: decreased Smad2 and Smad3 proteins Reduced caspase 3 activation: decreased cleaved caspase 3	[103]
In vivo/mice	Doxorubicin (3 mg/kg)	20(S)-ginsenoside Rh2 (Rh2) & 5, 10, 20 μM	Oral	Reduced cardiac damage markers: decreased serum CK and LDH at doses of 10 and 20 mg/kg Decreased AST levels at various doses of Rh2 Enhanced antioxidant defenses: increased SOD, CAT, and GSH Reduced oxidative stress: decreased MDA Protected myocardial cells: decreased histopathological changes	[69]

Table 4 (continued)

Study model	Chemotherapy drug (dosage)	Type of ginsenoside	Route of administration	Outcome	Refs.
In vitro/H9C2 cells,	Doxorubicin (1–2 μM)	20(S)-ginsenoside Rh2 (Rh2) and 5, 10, 20 μM	Pretreatment, intragastric, and injected	Increased cell viability at concentrations of 5, 10, and 20 μM Suggests that ginsenoside Rh2 may have a protective effect on cells and promote cell survival, which could be beneficial in reducing the cardiotoxic effects of doxorubicin	
In vitro/A549 cells	Doxorubicin (1–2 μM)	20(S)-ginsenoside Rh2 (Rh2) & 5, 10, 20 μM	In vitro incubation	Synergistically increased antitumor activity when combined with doxorubicin Suggests that ginsenoside Rh2 may be a useful adjunct therapy to enhance the effectiveness of doxorubicin in treating cancer while also reducing its cardiotoxic side effects	[69]

Conclusion

While chemotherapy-induced cardiotoxicity can be a serious issue, it is important to note that not all chemotherapy treatments carry this risk, and the benefits of cancer treatment often outweigh the potential heart risks. Ginseng, a traditional medicinal herb, has been suggested to have potential cardioprotective effects. Ginsenosides, the active compounds found in ginseng, are believed to have potential cardioprotective effects, which means they may help protect the heart from various forms of damage and disease. These effects are attributed to the diverse range of biological activities exhibited by different ginsenosides. The antioxidant activity of ginsenosides is believed to be a key mechanism behind their potential cardioprotective effects. The anti-inflammatory effects of ginsenosides are also believed to contribute significantly to their cardioprotective potential. Modulation of ion channels by ginsenosides is another important mechanism behind their potential effects on cardiovascular health, particularly regarding the regulation of blood pressure. Ginsenosides have also been suggested to potentially improve lipid profiles, which can have a positive impact on cardiovascular health. Ginsenosides have been found to exhibit anti-platelet and anti-thrombotic effects, which can contribute significantly to cardioprotection. The promotion of angiogenesis and neovascularization by ginsenosides also represents a therapeutic potential of these natural compounds in cardioprotection.

Limitations

While the existing evidence suggests that ginsenosides may have a cardioprotective effect in chemotherapy-induced cardiotoxicity, there are several limitations to the current research that need to be addressed. Firstly, the majority of studies on the cardioprotective effects of ginsenosides have been conducted in animal models or in vitro experiments, and there is a lack of clinical trials in human subjects. Therefore, the translational value of these findings to the clinical setting remains uncertain. Secondly, the current research on ginsenosides and chemotherapy-induced cardiotoxicity has primarily focused on a limited number of chemotherapeutic agents, especially doxorubicin. Further studies are needed to investigate the cardioprotective effects of ginsenosides in the context of other chemotherapeutic agents and treatment regimens. Thirdly, the potential interactions between ginsenosides and other medications, including chemotherapeutic agents, have not been well studied. Therefore, more research is needed to determine the safety and efficacy of ginsenoside treatment in combination with other therapies. Finally, the quality and consistency of ginsenoside preparations can vary widely depending on the source and method of extraction, which may impact their cardioprotective effects. Standardization of ginsenoside preparations and more rigorous quality control measures are needed to ensure the reliability and reproducibility of research findings. Overall, while the current evidence suggests that ginsenosides may have a cardioprotective effect in chemotherapy-induced cardiotoxicity, further research is needed to address these limitations and fully elucidate the therapeutic potential of ginsenosides in this context.

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Author contributions
In this study, all authors contributed to the design, writing, and review of the manuscript. HZZ managed and supervised the project. MTHG contributed to data collection and management. AA contributed to update of data and complete the final article. FSN contributed to search and data collection. HS contributed to search and data collection and editions of manuscript.

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Declarations

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