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REVIEW

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Cardioprotective effects of Ferulic acid against various drugs and toxic agents

Anandakumar Pandi[1*], Mahto Hemanti Raghu[1], Naveenkumar Chandrashekar[2] and Vanitha Manickam Kalappan[3]

Abstract

Background: Homeostatic regulation of cardiomyocytes is indispensable in maintaining the normal physiological activity of cardiac tissue. Cardiotoxicity induced by drugs may lead to cardiac abnormalities such as arrhythmia, myocardial infarction and myocardial hypertrophy. Moreover, drug-induced cardiotoxicity confines the additional use of the implicated drugs. Several studies have reported that consumption of phytochemicals on regular intervals shall protect humans against numerous diseases such as diabetes, cardiovascular disease, inflammatory diseases and cancer.

Main body: Ferulic acid (FA) is a plant derived polyphenol abundantly found in vegetables, fruits and grains. FA is widely known for its antioxidant, anti-inflammatory, anticancer, nephroprotective and hepatoprotective effects. FA has been well documented for its cardioprotective activity against various drugs and toxic agents as well. However, the cardioprotective action of FA have remained a challenge with regard to understanding its mechanism in health and diseases.

Conclusion: The main purpose of this review is to explore the cardioprotective mechanisms of FA against several drugs and chemicals to recommend further studies to investigate the potential protective effect of FA.

Keywords: Ferulic acid, Antioxidant, Cardioprotective, Preclinical, Cell line, Human health

1 Background

Cardiotoxicity usually denotes toxicity that has a harmful effect on the heart, which may ultimately result in myocardiopathy such as arrhythmia, myocardial infarction and myocardial hypertrophy [1, 2]. In the last few years, more than 20% of clinical drugs were forced out of the market because of cardiovascular side effects, which hampered the drug development and extremely affected the improvement in patient health [3]. Several studies have showed that drug-induced cardiac dysfunction may be a stepwise process accompanied by the increase of cardiac biomarkers and structural myocardial deformation, finally resulting in reduced left ventricular ejection fraction (LVEF) [4, 5]. Recently, the most accepted term for cardiotoxicity is the reduction in LVEF of at least 10% to less than 55% [6]. Studies show that cardiac cell death or damage concurrently occurs with the progression of cardiotoxicity, demonstrating that drug-induced cardiomyocyte death may be the major reason for cardiotoxicity [7].

In the recent years, extensive research has been undertaken to investigate the action of phytochemical compounds found in the diet [8]. They are commonly found in fruits, vegetables, beverages and herbal remedies [9]. These alkaloid compounds contain numerous active substances like flavonoids, polyphenols, indoles and sulfur containing elements [10]. These phytochemicals have the tendency to safeguard humans against diabetes mellitus, hepatic disorders, cardiovascular disease, cancer, arthritis, and Alzheimer's disease and many more [11, 12]. Findings from numerous studies have demonstrated that

*Correspondence: bioanand77@gmail.com

[1] Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Deoghar, Jharkhand, India
Full list of author information is available at the end of the article

phenolic compounds are generally non-toxic when taken in smaller quantities and they possess extraordinary therapeutic values. [13, 14].

Ferulic acid (FA) is a polyphenol that is found in many staple foods such as grain bran, whole grain foods, citrus fruits, banana, coffee, orange juice, eggplant, bamboo shoots, beetroot, cabbage, spinach and broccoli [15]. FA exhibits an extensive range of therapeutic functions against diabetes [16], cancer [17], renal toxicity [18], liver toxicity [19], cardiotoxicity [20] and neurotoxicity [21].

In this review, the cardioprotective effects of FA against various drugs and toxins have been described in a comprehensive manner.

2 Main text

2.1 Sources

Ferula foetida is the primary source of 3-methoxy-4-hydroxycinnamic acid that was isolated first [22]. The chief sources of FA include rice, wheat and oats [22, 23]. Other sources of ferulic acid are fruits and vegetables [22, 23]. In some vegetables and fruits such as in coffee, cabbage, celery and carrots, FA is found to be in its conjugated form with hydroxyl acids. In grains, FA may form an ester with sterols. Forty to ninety percent of free FA is present in some vegetables such as burdock, water dropwort and eggplant [24, 25]. Additionally, 0.1–0.5% free FA is present in cereals [25].

2.2 Chemistry

Ferulic acid (FA) is the common name for 3-(4-hydroxy-3-methoxyphenyl)-2- propenoic acid. Other names include 3-methoxy-4-hydroxycinnamic acid, caffeic acid 3-methyl ether, and coniferic acid [26] (Fig. 1). Ferulic acid isolated from plants usually exists as the trans isomer. Due to its phenolic nucleus and an extended side chain, FA readily forms a resonance stabilized phenoxy radical which accounts for its free radical-scavenging effect [27].

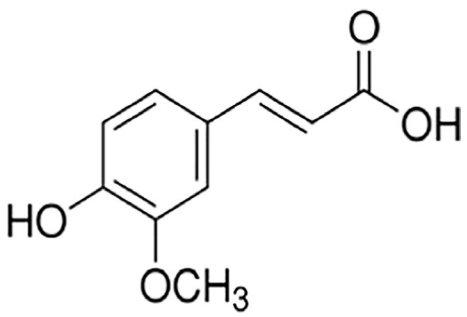

Fig. 1 Structure of Ferulic acid

2.3 Bioavailability and metabolism

Several studies on absorption of FA have reported that FA can be absorbed from the stomach [28], jejunum [29] and ileum [30]. FA may be transported across the intestinal brush border membrane via carrier mediated sodium-dependent transport mechanism [31]. The amount of FA intake via consumption of cereals, vegetables, fruits, coffee and juices may reach up to 150–250 mg/day [30]. FA metabolites commonly found in circulation are FA-glucuronide, FA-sulfate, FA-diglucuronide, FA-sulfoglucuronide (FA-diconjugate with sulfate and glucuronide), m-hydroxyphenylpropionic acid, feruloylglycine, dihydroferulic acid, vanillic acid and vanilloylglycine [31]. Conjugated FA such as FA-glucuronide, FA-sulfate and FA-sulfoglucuronide are the predominant metabolites in the plasma and urine of rats [32]. It is reported that the bioavailability of FA is much greater compared to other dietary flavonoids and monophenolics. FA remains in blood for a longer time than other antioxidants like ascorbic acid [33].

2.4 Cardioprotective activity of FA

2.4.1 Effect of FA on Isoproterenol induced cardiotoxicity

Isoprenaline or isoproterenol (ISO) is a drug commonly employed for the treatment of bradycardia, heart block and sometimes for asthma [34]. It is categorized under non-selective β adrenoceptor agonist, which is the isopropylamine analog of adrenaline [35]. ISO acts as a synthetic β-adrenergic receptor agonist. One of the most common side effects of ISO is cardiotoxicity [36].

Several studies have shown the effect of FA on ISO induced cardiotoxicity [37–41]. Different doses of ISO (85, 150 mg/kg body weight) were used in these studies for inducing cardiotoxicity. FA (10, 20 and 40 mg/kg body weight) was given orally to see its protective effect. ISO induced rats showed abnormal alterations in oxidative stress parameters such as MDA, TBARS along with reduction in cellular antioxidants such as SOD, CAT, GPx, GST and GSH; activities of liver enzymes such as AST, ALT, CPK and LDH, pro-inflammatory cytokines TNF-α, IL-β and IL-6; serum-free cholesterol, esterified cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol and total cholesterol. Further, mitochondrial damage in ISO induced cardiotoxicity induced rats revealed alterations in the activities of TCA cycle and respiratory chain enzymes such as ICDH, SDH, MDH, αKGDH, NADH dehydrogenase and cytochrome C oxidase. In addition, the activities of serum lysosomal hydrolases such as β-D-glucuronidase, β-D-galactosidase, β-D-N acetyl glucosaminidase, cathepsin D and acid phosphatase were significantly increased in ISO induced animals. Further, the levels of

Na^+, Ca^{2+} were increased and K^+ was decreased in the heart of ISO induced rats. All these abnormalities were markedly improved upon FA treatment revealing its strong hepatoprotective activity. The antioxidant, antihyperlipidemic, anti-inflammatory and mitochondrial stabilizing potential of FA were found to be key factors for its cardioprotective function.

In another study, Zhang et al. [42] have reported the effect of FA on ISO induced cardiotoxicity in Sprague Dawley rats. ISO (150 mg/kg body weight) was administered by intraperitoneal route for two days to induce cardiotoxicity. FA (5, 25 and 50 mg/kg body weight) treated rats effectively modulated heart rate, ejection fraction % (EF), fractional shortening (FS), and decreased left ventricular posterior wall thickness at end-systole (LVPWS), left ventricular internal diameter (LVID) along with decreased plasma NT-pro BNP levels. TUNEL assay and immunoblotting analysis were performed to highlight the effect of FA on apoptosis. Additionally, FA treatment effectively activated Nrf2 signaling pathway by significantly increasing the protein expressions of p-Nrf2, HO-1, NQ01 and decreasing the expression of Keap 1 compared to the ISO induced group. Reducing oxidative stress, apoptosis and activating Nrf2 signaling pathway was important for the cardioprotective efficacy of FA against ISO induced cardiotoxicity.

2.4.2 Effect of FA on Doxorubicin induced cardiotoxicity

Doxorubicin (DOX) is an anthracycline antibiotic used to treat various types of cancer, including solid tumors, hematologic malignancies and soft tissue sarcoma [43]. It acts by intercalating DNA and by arresting DNA replication by inhibiting topoisomerase II. The most deleterious effect of DOX is dilated cardiomyopathy leading to congestive heart failure [44].

A single intraperitoneal dose of DOX (20 mg/kg body weight) induced cardiotoxicity in Wistar rats [45]. FA was given at different doses of 20, 40 mg/kg body weight for 7 days orally to evaluate its effects. DOX's cardiotoxicity was revealed by abnormal increase in serum CK-MB, LDH, IL-1β, and IL-6; enhanced activities of Mg^{2+}ATPase, Ca^{2+}ATPase and altered gene expressions of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Histological analysis showed increased fibrosis and collagen deposition in the cardiotoxicity induced rats. FA treatment was able to revert all the above alterations seen during DOX induced cardiotoxicity. Modulation of oxidative stress, inflammation, ER stress, calcium homeostasis and renin played a major role in the cardioprotective efficacy of FA against DOX induced cardiotoxicity.

2.4.3 Effect of FA on Cyclophosphamide induced cardiotoxicity

Cyclophosphamide (CP) is a widely used chemotherapeutic agent belonging to the class of alkylating agents [46]. It is used to treat variety of cancers like lymphoma, leukemia and multiple myeloma. It is also used as an immune suppressive agent in graft-vs-host disease [47]. Administration of large dose of CP has been reported to cause hemorrhagic cell death, leading to heart failure [48].

Song et al. reported the influence of FA (200 mg/kg body weight) on CP induced cardiotoxicity in ICR mice [49]. Serum biomarkers such as ALT, AST, CK and LDH were increased, hematological parameters such as total WBC count, RBC count, hemoglobin and platelets were reduced; the levels of pro-inflammatory cytokines such as TNF-α, IL-β and IL-6 were markedly increased in animals with cardiac damage caused by CP. Further, the protein expression of p-NF-kB, p-IkBα, p-IKkα and IKkβ were significantly increased in CP challenged groups. FA (50 & 100 mg/kg body weight) intragastric treatment effectively regulated all the above alterations. This study showed that FA effectively ameliorated CP induced cardiotoxicity in mice by inhibiting IKk/IkB/NF-kB pathway and by reducing inflammation.

2.4.4 Effect of FA on Arsenic induced cardiotoxicity

Arsenic (Ars) is a naturally found metalloid that is universally present in both organic and inorganic forms. People are exposed to high levels of inorganic arsenic through contaminated drinking water, and food crops irrigated with excessive arsenic water sources. Ars exposure increases the risk of ischemia, arrhythmia and heart failure [50].

This study showed the protective function of FA on Ars induced cardiotoxicity in Wistar rats [51]. Sodium arsenite (5 mg/kg body weight) was dissolved in distilled water and administered orally for 30 days to induce cardiac damage. FA (10, 20 & 40 mg/kg body weight) was also supplemented orally as a treatment drug for 30 days to see its effect. The key parameters modulated by FA include serum cardiac markers such as CK-MB, LDH and ALT; protein carbonyls, LPO in myocardium and cellular antioxidants (SOD, CAT, GPx, GSH, ascorbic acid). Moreover, FA treatment modulated the protein expression of cytoskeleton intermediate filament proteins such as desmin, vimentin and AMPK signaling proteins such as pAMPKα, pAMPKβ (1/2), pACC. The modulatory role of FA against Ars induced cardiotoxicity could be because of its ability to improve antioxidants, ATP levels and modulation of AMPK signaling pathway.

Another study [52] reported the protective effects of FA in Ars induced cardiotoxicity in a Zebrafish model. Cardiotoxicity was induced by exposing to 1 mM Ars. FA supplementation (30 μM) markedly alleviated the changes in heartbeat, malformations such as pericardial edema, yolk sac edema, dorsal curvature, flat-head, and eye defects. Moreover, mRNA expression levels of some of the major genes of cardio genesis such as nkx2.5, bmp2b, myh6, gata4, gata5, myl7, and tnnt2 were appreciably regulated by FA. The cardioprotective function of FA reported in this study could be by modulating oxidative stress and regulating cardio genesis against Ars induced cardiotoxicity in Zebrafish model.

2.4.5 Effect of FA on streptozotocin induced diabetic cardiopathy

Streptozotocin (STZ) belongs to the class of glucosamine-nitrosourea compound. STZ is an alkylating antineoplastic agent that is mainly toxic to the pancreas and is widely used in experimental research for inducing type 1 or type 2 diabetes [53].

In this study, Wistar rats were induced with single intraperitoneal injection of STZ (50 mg/kg body weight) to induce hyperglycemia [54]. FA (50 mg/kg body weight) was supplemented orally for 8 weeks to assess its beneficial effect. Hyperglycemia induced rats showed abnormal variations in blood glucose, serum insulin levels, LPO and cellular antioxidants SOD, CAT, GR and GSH/GSSG ratio along with abnormalities in plasma total cholesterol, triglycerides and HDL cholesterol. In addition, the protein expression of insulin signaling proteins such as PI3K, Akt, GSK-3β, GLUT-4 and ER-stress dependent apoptotic cell death proteins such as calpain-1, cleaved caspase 12, GRP78, CHOP, cleaved caspase 3, cleaved PART and p-eIF2α/total eIF2α ratio were altered in STZ induced rats. FA supplementation effectively modulated all these changes. The findings of this study showed that FA alleviated STZ induced diabetic cardiopathy by modulating oxidative stress, hyperlipidemia and regulating PI3K/Akt dependent signaling cascade.

2.4.6 Effect of FA on N (ώ)-nitrol-L-arginine methyl ester induced cardiotoxicity

It is well recognized that nitric oxide (NO) produced in vascular endothelial cells has a potent vasodilator effect and plays an important role in vascular resistance and growth [55]. Administration of L-arginine analogues like N (ώ)-nitrol-L-arginine methyl ester hydrochloride (L-NAME) suppresses NO biosynthesis, resulting in hypertension and cardiac injury [56].

The effect of FA on L-NAME induced cardiotoxicity in male Wistar rats has been reported [57]. L-NAME (50 mg/kg body weight) was administered orally for eight weeks. FA (0.8 g/kg of powdered food) mixed with feed was supplemented parenterally. Major factors modulated by FA in this study include blood pressure, left ventricular weight, MDA, nitric oxide, MnSOD. Further, FA treatment reduced inflammatory cell infiltration, ferric iron accumulation, and collagen deposition in left ventricles and kidneys. The cardioprotective role of FA reported in this study is through its potent antioxidant and anti-inflammatory activity.

2.4.7 Effect of FA on TNF-α/cycloheximide-induced cardiac apoptosis

Cycloheximide (CHX) is a fungicide produced by *Streptomyces griseus* that is commonly used in research to hinder protein synthesis in eukaryotic cells [58]. TNF-α produces a sequence of biological effects that include immuno stimulation, mediation of host resistance to bacteria, activation of protein kinase C, and activation of the expression of a wide variety of genes generally involved in inflammation or cell growth [59, 60].

The protective efficacy of FA against TNF-α (TNFA)/cycloheximide (CHX) -induced apoptosis in H9c2 cardiomyocytes as well as in acute myocardial infarction (AMI) induced C57BL/6 mice model has been reported [61]. In H9c2 cells, the concentration of TNFA was 10 ng/mL and CHX was 5 μg/mL were used. Anti-apoptotic effect of FA (50 μM) was evident through its ability to decrease the number of apoptotic cells and to reduce the levels of cleaved caspase-3 compared to the TNFA/CHX treated cells. Further, FA effectively modulated the levels/protein expressions of chief autophagy signaling proteins such as Akt/mTLC3B, p62 LC3B-II and LC3B1. In the in vivo study, FA was dissolved in saline and given by oral gavage route for 4 weeks at different doses (125 mg/kg/d, 62.5 mg/kg/d and 31.25 mg/kg/d) for 28 days to assess its protective role. The findings of the study clearly demonstrated that FA reduced oxidative stress induced autophagy and suppressed apoptosis by regulating Akt/mTOR signaling pathway.

2.4.8 Effect of FA on hydrogen peroxide and isoprenaline induced toxicity

The cardioprotective role of FA by modulating hydrogen peroxide and isoprenaline induced oxidative stress was reported [62]. In the cell line study, H9c2 cardiomyocytes were subjected to treatment by H_2O_2 (200 μM) to induce oxidative stress. FA (50 μM) treated cells showed reduced oxidative stress and decreased apoptosis. Moreover, FA treatment modified apoptosis and miR-499-5p/p21 pathway related proteins such as Bax, p-p38, cleaved caspase 3, Bcl-2 and p21. The in vivo study was carried out in the C5/BL/6 J mice heart injury model. Oxidative stress was induced using isoprenaline (IPL) (30 mg/kg body weight) per day in saline for 14 days. FA (30 mg/

Table 1 Summary of the cardioprotective effects of Ferulic acid against various drugs and chemicals

S.No	Author	Year	Model used	Cardiotoxic agent	Dose of Ferulic acid used	Major Mechanism/ Effect	Reference
1	Yogeeta et al	2006	Wistar albino rats	Isoproterenol	20 mg/kg body weight	Reducing oxidative stress and improving cellular antioxidants	[37]
2	Yogeeta et al	2006	Wistar albino rats	Isoproterenol	20 mg/kg body weight	Reducing lipid peroxidation and modifying lipid and lipoprotein metabolism	[38]
3	Yogeeta et al	2006	Wistar albino rats	Isoproterenol	20 mg/kg body weight	Improving mitochondrial stability by decreasing oxidative stress and increasing mitochondrial antioxidants	[39]
4	Yogeeta et al	2006	Wistar albino rats	Isoproterenol	20 mg/kg body weight	Cytoprotective effect by modulating membrane bound phosphatases and lysosomal hydrolases	[40]
5	Jain et al	2018	Sprague Dawley rats	Isoproterenol	10, 20 and 40 mg/kg body weight	Reducing oxidative stress and inflammation	[41]
6	Zhang et al	2021	Sprague Dawley rats	Isoproterenol	5, 25 and 50 mg/kg body weight	Reducing oxidative stress, regulating apoptosis and activating Nrf2 signaling pathway	[42]
7	Aswar et al	2019	Wistar albino rats	Doxorubicin	20, 40 mg/kg body weight	Modulation of oxidative stress, inflammation, ER stress and calcium homeostasis	[45]
8	Song et al	2016	ICR mice	Cyclophosphamide	50 and 100 mg/kg body weight	Suppressing IKk/IkB/ NF-kB pathway and reducing inflammation	[49]
9	Pannerselvam et al	2020	Wistar albino rats	Arsenic	10, 20 and 40 mg/kg body weight	Restoring cellular antioxidants, ATP levels and modulation of AMPK signaling pathway	51
10	Perumal et al	2021	Zebrafish	Arsenic	30 µM	Modulating oxidative stress and regulating cardio genesis	52
11	Chowdhury et al	2016	Wistar albino rats	Streptozotocin	50 mg/kg body weight	Modifying oxidative stress, hyperlipidemia and regulating PI3K/Akt dependent signaling cascade	54
12	Alam et al	2013	Wistar albino rats	N(ώ)-nitrol-L-arginine methyl ester hydrochloride	0.8 g/kg of food	Decreasing oxidative stress, preventing inflammation and increasing antioxidant s	57
13	Li et al	2020	H9c2 cells/ C57BL/6 mice	TNF-alpha/Cycloheximide	50 µM	Reducing oxidative stress and stimulating autophagy by regulating Akt/mTOR signaling pathway	61
14	Sun et al	2021	H9c2 cells/ C5/BL/6 J mice	Hydrogen peroxide/ Isoprenaline	50 µM/30 mg/kg body	By modulating miR-499-5p/p21 signaling pathway	62

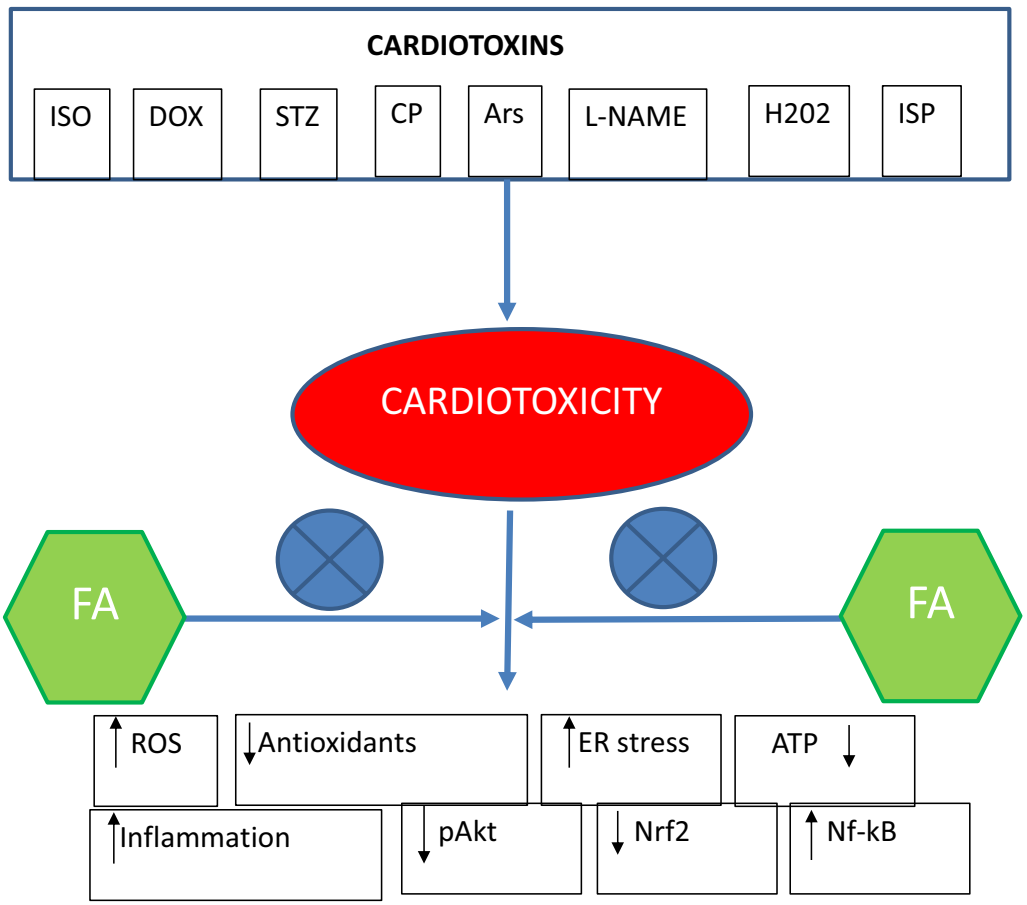

Fig. 2 Molecular mechanism showing the cardioprotective effect of Ferulic acid against various drugs and toxic agents

kg body weight) treatment efficiently attenuated all the abnormalities caused by IPL induced cardiotoxicity. In addition, FA treatment regulated the mRNA expression of miR-499-5p and p21. The results of the study showed that FA treatment effectively controlled oxidative stress induced by H_2O_2 and IPL by regulating the miR-499-5p/p21 signaling pathway both in vitro and in vivo.

2.5 Clinical studies on FA

The studies of FA on human subjects are limited. A study by Bumrungpert et al. [63] showed that FA treatment (1000 mg/day) for six weeks improved lipid profiles, oxidative stress, oxidized LDL-C and inflammation in patients with hyperlipidemia. In another study, laser-assisted delivery of FA along with vitamin C and E was found to be helpful in wound healing [64]. A study from Wu et al. proved that topical antioxidant complex containing vitamins C, E and FA can protect solar-simulated ultraviolet irradiation induced acute photodamage in human skin [65].

2.6 Toxicity of FA

FA was found to be well tolerated in most of the animal studies. Investigations have shown that oral dose of FA up to 150 mg/kg body weight was tolerable in rats and did not induce any toxic effects [38, 42]. A study by Xu et al. reported that intravenous administration of FA (866 ± 28 mg/kg) to mice resulted in spasticity, tremor, ankylosis of hind limbs and death within 6 h [66] Additionally, a study from Peng et al. displayed that long-term administration of FA may cause renal damage; however, the mechanism is unclear [67]. In vitro studies showed that FA (300 µg/mL) treatment had no noticeable toxicity to red blood cells, platelets and white blood cells [68]. Truzzi et al. reported that FA (40 mg/L) elicited toxic effects in human monocytes (U937) and human colon cancer cells [69]. In human studies, a dosage of 1000 mg/day has been found to be safe and tolerable [63].

3 Conclusions

This review has briefed the cardioprotective effects of FA against cardiotoxicity induced by various drugs and chemical agents using preclinical studies and cell line models (Table 1) (Fig. 2). It is understood that FA was basically involved in regulating ROS mediated oxidative stress, cellular antioxidants, apoptosis, inflammation, autophagy and energy metabolism in most of the studies. Some of the major signaling pathways regulated by FA were Nrf2 signaling pathway, Akt/mTOR signaling pathway, PI3K/Akt dependent signaling, AMPK signaling and miR-499-5p/p21 pathways. It is also to be recalled that most of the studies to assess the cardioprotective effects of FA were demonstrated in animals (rats, mice, zebrafish) and cell line models; cardioprotective role of FA in human subjects is extremely limited. Therefore, the bioavailability, toxicity and mode of administration of FA requires further research and development. Moreover, since most of the findings reported in the current work are based on animal studies, extensive research on human subjects would be highly recommended in order to implement this compound as a potential cardioprotective agent.

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AP searched the literature, and designed the manuscript. MHR and VMK participated in discussions and suggested useful additions in the manuscript. NC helped in preparing the tables and figures. All authors read and approved the final manuscript.

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All authors give their consent for publication in this journal.

Competing interests
Authors declare that there are no competing interests.

Author details
[1]Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Deoghar, Jharkhand, India. [2]Department of Biochemistry, Indian Academy Degree College - Autonomous, Meganahalli, Hennur Main Road, Bangalore, Karnataka, India. [3]Department of Medical Biochemistry, University of Madras, Taramani Campus, Chennai, Tamilnadu, India.

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