An audit of cardio protective natural products

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ABSTRACT:
Cardiovascular Diseases (CVDs) accounts for approximately 30% of overall death worldwide. There are various CVDs among which Myocardial Infarction (MI) and stroke are found to be the major contributor to mortality. Adrenaline and isoprenaline are the catecholamines used in various cardiovascular interventions. However, toxic doses cause stress on the myocardium causing necrosis in the cardiac muscles. It is discovered that pathophysiological and morphological alterations observed in these catecholamines overdose are similar to changes in MI in humans. Hence, they are considered as reliable model to investigate protective effect in case of heart attack. Doxorubicin belongs to the class of anthracycline antibiotic, which is most widely used in the treatment of range of cancers such as leukemias, lymphomas, sarcomas, solid tumors etc. Despite its widespread use it produces dose dependent selective cardiotoxicity via the formation of reactive oxygen species (ROS). Dexrazoxane is the only approved drug by USFDA to alleviate DOX induced cardiotoxicity, the drawback is that it interferes with the clinical activity of DOX. Paradoxically, researchers investigated the potential of phytochemicals such as Curcuma longa, Allium sativum, Coleus forskohlii, Syzygium aromaticum, Crocus sativus etc. against drugs induced cardiotoxicity. Unlike synthetic drugs, phytochemicals from natural products are safe for long term use. The present article reviews possible mechanisms of inducing agents, changes in parameters and cardioprotective effects of various plant species against drugs induced cardiotoxicity.

***KEYWORDS*: Cardiovascular Diseases,Myocardial Infarction, Catecholamine, Cardio protective, Evaluation Parameters, Natural Products, Anthracyclines**

CONTENTS

1. INTRODUCTION

Cardiovascular disease (CVD) is a series of disorders affecting the heart and blood vessels, including peripheral arterial disease, coronary heart disease (CHD) and congestive heart failure (CHF) etc[1]. Currently, CVD accounts for ~30% of death worldwide, including nearly 40% in high-income countries and about 28% in low- and middle-income countries[2].

Myocardial infarction (MI) is described as the loss of myocardial cells as a result of a mismatch between oxygen demand and supply in the heart[3]. Isoprenaline is a synthetic sympathomimetic nonselective β-adrenergic agonist. It is mainly used in the treatment of bradycardia, thioridazine-induced torsade de pointes, and heart block[4]. However, toxic dosescause severe stress on the myocardium causing infract-like necrosis of the heart muscle. It is well established that pathophysiological and morphological alterations observed in ISO-induced cardiac dysfunctions in animal experiments are similar to the changes in humans MI[5].

Adrenaline(Adr)affects the heart in both inotropic and chronotropic ways. Excess catecholamine has been shown to cause coronary vasoconstriction, which causes an increase in the demand for oxygen by heart cells and a decrease in myocardial blood flow, resulting in acute cardiotoxicity. Adr-stimulated cardiotoxicity is mediated by an increase in free radical production and a decrease in heart anti-oxidants, resulting in oxidative stress and as a result, cardiac tissue necrosis or death[3].

Doxorubicin (DOX) is a cytotoxic anthracycline antibiotic that is used to treat a variety of cancers, including solid tumors, soft tissue sarcomas, and hematological malignancies[6]. However, due to the risk of dose-dependent cardiotoxicity, which can result in irreversible cardiomyopathy and congestive heart failure, clinical use of this medicine has been limited[7]. The principal anticancer mechanism of DOX is through DNA chelation, which further inhibits the progression of topoisomerase II and then produces free radicals to kill cancer cells. However, this effect is not selective for cancer cells alone as healthy normal cells can also be affected by the same mechanism[6].

The formation of reactive oxygen species (ROS) by doxorubicin during its intracellular metabolism causes cardiotoxicity. ROS causes oxidative damage to essential cellular components and membranes by causing lipid peroxidation, which results in permanent myofibril loss, sarcoplasmic reticulum dilation, cytoplasmic vacuolization, and mitochondrial swelling[8].

Induction of free radicals and other toxic nonradicals released from cells by catecholamines and anthracyclines can be neutralized by generating endogenous antioxidants or by introducing exogenous antioxidants in nutritional supplements. These interventions may prevent or ameliorate the toxic effects of drugs[6].

Medicinal plants, plants-based foods and their constituents have received great attention for their salutary effects and potential to treat many aspects of ischemic heart disease or MI. Similarly, the use of herbs in pharmacotherapy is on the rise, owing to a growing understanding that herbal products can affect the course of cardiac disease and can give an integrated approach of nutritious elements that aid in the restoration and maintenance of balanced bodily systems[9].

2. MECHANISM OF CARDIOTOXICITY

2.1 DOXORUBICIN

A) Mitochondrial dependent reactive oxygen species

One of the subcellular organelle modifications after doxorubicin-induced cardiotoxicity is mitochondrial abnormalities in cardiomyocytes. The mitochondria produce 90 percent of the ATP used by cardiomyocytes. Cardiolipin, a component of the inner mitochondrial membrane, plays a critical role in the progression of doxorubicin-induced pathologies. Cardiolipin and doxorubicin have a mutual attraction because cardiolipin has an anionic charge and doxorubicin has a cationic charge. Doxorubicin and cardiolipin form an irreversible combination as a result[10].

Cardiolipin is required for the activation of electron transport chain enzymes including cytochrome C oxidase, NADH cytochrome C oxidoreductase, and others. Cardiolipin is unavailable for activating the above-mentioned enzymes, which are key components of the electron transport chain's complex II and complex IV because it is already bound to doxorubicin[11].

B) Role of Iron regulatory protein in the production of reactive oxygen species[12]

Fe3+ (ferric iron) interacts with the ketone and hydroxy group of doxorubicin to create doxorubicin-Fe2+ free radical complexes in a non-enzymatic process. Doxorubicin raises the intracellular iron pool, which is implicated in the production of free radicals in normal circumstances.

C) Role of Nitric Oxide in the production of reactive oxygen species[13]

Nitric oxide is found in higher quantities in the diseased heart. During doxorubicin treatment, the level of iNOS, as well as the amount of NO, increases in cardiac cells. The production of superoxide anions by activated NOXs combines with NO during doxorubicin therapy, resulting in the synthesis of peroxynitrite via lipid peroxidation. Peroxynitrite oxide production causes mitochondrial oxidative stress, apoptosis, and necrosis.

D) Role of nrf2 in oxidative stress[14]

The basic leucine zipper protein nuclear factor erythroid 2-related factor 2 (Nrf2) is involved in the regulation of the expression of a variety of antioxidant proteins. In doxorubicin-induced cardiomyopathy, Nrf2 is also important. Cardiotoxicity and cardiac function are worsened by Nrf2 deficiency.

2.2 ISOPRENALINE (ISP)[4]

ISP, a synthetic catecholamine causes toxicological alterations in heart tissue by producing oxidative stress, which causes antioxidant enzymes to be depleted. ISP also reduces oxygen delivery, which leads to myocardial hypoxia and necrosis. Cellular permeability is increased as a result of increased lipid peroxidation, which leads to ventricular hypertrophy. When phospholipase is activated, it immediately produces inflammation and ST segment elevation, resulting in acute heart damage and myocardial ischemia.

NF-κB and mitogen activated protein kinases (MAPKs) like p38, as well as other signalling pathways, are activated, accelerating cellular death. All of these processes, when coupled, form the hallmarks of ISP-induced toxicity, which, if left untreated, can lead to cardiac fibrosis.

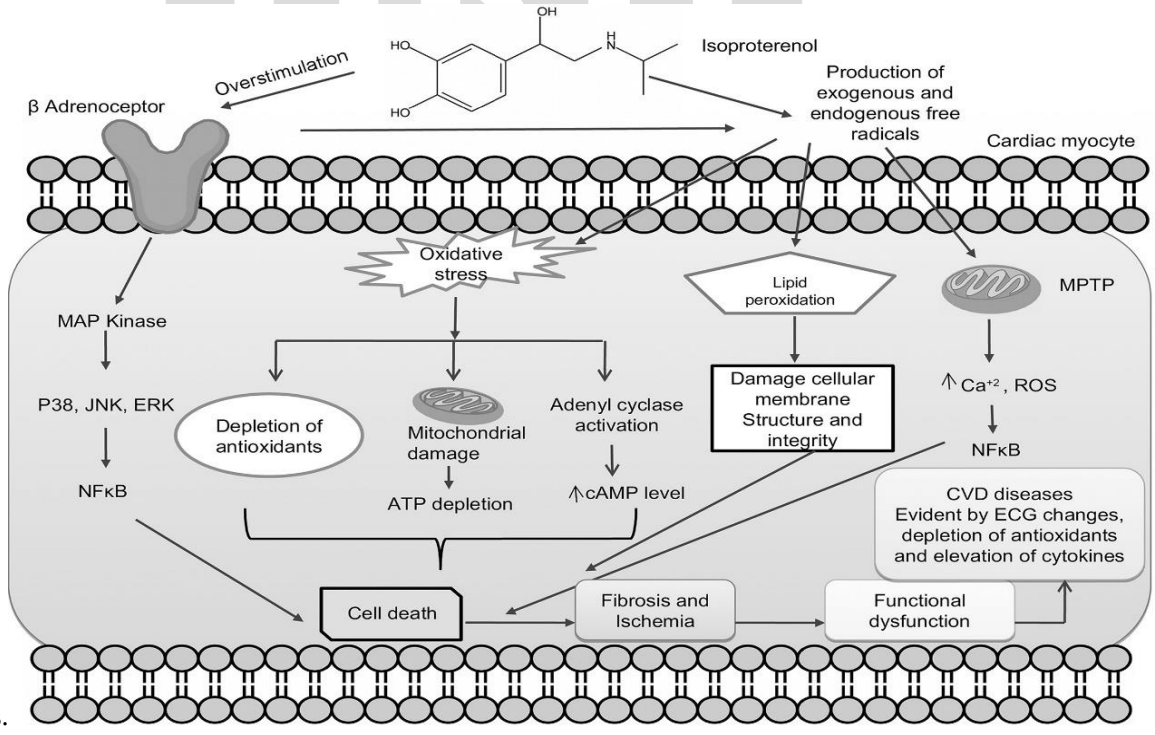

Fig 1: Fig 1 represents the molecular mechanism of Isoprenaline induced cardiotoxicity and the central role of oxidative stress in producing cell death.

Abbreviations: MAP: Mitogen Activated Protein, JNK: Janus Kinase, ERK: Extracellular Regulated Kinase, NFκB: Nuclear Factor Kappa B, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, cAMP: cyclic Adenosine Mono Phosphate, ATP: Adenosine Tri Phosphate, Ca^{2+}: Calcium, ROS: Reactive Oxygen Species

2.3 ADRENALINE[15]

Catecholamines such as epinephrine and norepinephrine function as neurotransmitters. These catecholamines are released in response to stressful events. Catecholamines have a favourable effect on the cardiovascular system and the body's total energy requirement at first. Long-term elevations of catecholamines in the circulation, on the other hand, might have negative consequences, particularly for the heart.

Relative hypoxia, hemodynamic changes, coronary insufficiency, metabolic changes (lipid and energy balance), electrolyte changes, membrane permeability changes, and intracellular Ca^{2+} overload are all thought to play a role in catecholamine-induced cardiotoxicity. Cardiotoxicity is thought to be caused by oxidative stress (e.g. free radical processes) and oxidative catecholamine metabolites (e.g. aminochromes)

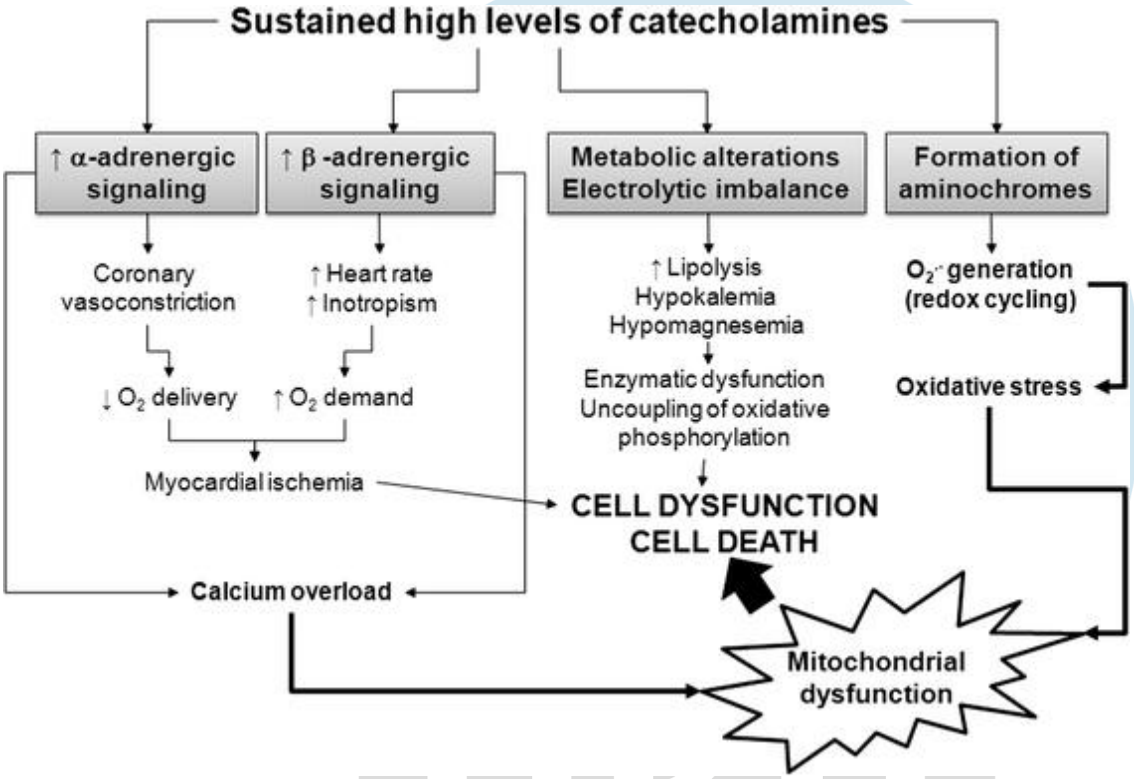

Fig 2: Fig 2 represents the possible mechanisms of adrenaline mediated cellular dysfunction

3. EVALUATION PARAMETERS

Table 1

3.1 Serum Parameters

Blood samples are collected from the retro-orbital vein of rats using a glass capillary tube. The blood samples were let to coagulate and then they were centrifuged, serum is separated and following parameters are estimated.

SL NO	PARAMETER	ABBREVATION	DESCRIPTION
1	Cardiac Troponin I	CTnI	Cardiac regulatory proteins that control the calcium-mediated interaction between actin and myosin
2	CardiacTroponin T	CTnT	Cardiac regulatory proteins that control the calcium mediated interaction between actin and myosin
3	Creatine phosphokinase-MB	CK-MB	Catalyzes the phosphorylation of creatine which is a high energy compound for muscle contraction
4	Lactate dehydrogenase	LDH	Enzyme catalyzes of pyruvate to lactate (glycolysis), which plays an important role in cellular respiration
5	Aspartate aminotransferase	AST	Amine group transfer catalysis between glutamate to aspartate
6	Alanine aminotransferase	ALT	Amine group transfer catalysis between glutamate to alanine
7	Alkaline Phosphatase	ALP	Catalyzes the breakdown of phosphate from the complex
8	High density lipoprotein	HDL	Good cholesterol-absorbs cholesterol and carries it back to the liver

9	Low density lipoprotein	LDL	Transport cholesterol from its site of synthesis in the liver to the various tissues and body cells
10	Very low density lipoprotein	VLDL	It is made in the liver and is responsible for delivering triglycerides to cells
11	Interleukin-1 beta	IL-1β	Cytokine required for activating the innate immune response
12	Metalloproteinase-9	MMP-9	Degrades extracellular matrix (ECM) proteins and activates cytokines and chemokines to regulate tissue remodeling
13	Vascular Endothelial Growth Factor	VEGF	Key regulator of physiological angiogenesis during embryogenesis, skeletal growth, and reproductive functions.
14	Interleukin-6	IL-6	Pro-inflammatory cytokine that induces final maturation of B-cells
15	Interleukin-10	IL-10	Anti-inflammatory cytokine that plays a role in inhibiting the host immune response to pathogens
16	Angiotensin-Converting Enzyme	ACE	Blood pressure regulating enzyme by converting angiotensin-1 to angiotensin-2
17	High sensitive C reactive protein	HsCRP	Protein made in the liver, sent to bloodstream in response to inflammation
18	Creatine kinase	CK	Catalyzes the phosphorylation of creatine which is a high energy compound for muscle contraction
19	Total cholesterol	TC	Type of lipid comprising the amount of HDL, LDL, and TG in blood
20	Myoglobin	MYO	Protein found in striated muscles (skeletal muscle and heart muscle). Higher levels in serum indicate severe muscle injury
21	Trasforming growth factor-β1	TGF-β1	Cytokine that plays an important role in angiogenesis, immunoregulation, etc. It also exerts powerful anti-inflammatory function
22	8-hydroxyguanosine	8-OHdG	Oxidative derivative of guanosine which is used as a biomarker of oxidative stress causing RNA damage
23	Quinone reductase	QR	The intracellular cytosolic enzyme which catalyzes the reduction of quinones
24	Nuclear factor erythroid related factor-2	Nrf-2	Controls the expression of genes whose protein products are involved in detoxification and elimination of ROS
25	Heme Oxygenase-1	HO-1	Nrf2 regulated gene that plays a critical role in the prevention of vascular inflammation.
26	Atrial Natriuretic Peptide	ANP	Peptide hormone secreted from cardiac atria functions to lower BP and electrolyte homeostasis
27	Brain Natriuretic Peptide	BNP	Hormone of cardiac origin that plays an important role in regulating intravascular blood volume and vascular tone
28	β-Myosin Heavy Chain	β-MHC	Actin based motor protein expressed primarily in the heart. It plays a major role in cardiac muscle contraction
29	Procollagen type I N-terminal propeptide	P1NP	Formed in fibroblasts and converted to collagen by peptidases, most commonly found in mineralized bone
30	Procollagen type III N-terminal propeptide	P3NP	It is an extension peptide that is cleaved and liberated into extracellular fluid and is a serum biomarker of collagen turnover
31	α-LIPOIC ACID	ALA	Anti-oxidant made by the body also plays a role in converting glucose to energy
32	Ascorbic acid	VIT C	Water-soluble vitamin required for tissue repair, collagen formation, and enzymatic production of certain neurotransmitters
33	Alpha-Hydroxybutyric Dehydrogenase	α-HBDH	High energy compound that provides energy when not enough carbohydrates have been taken. It is also a diagnostic biomarker in insulin resistance
34	Blood Urea Nitrogen	BUN	Product produced by protein metabolism and found abundantly in urine
35	Uric acid	UA	Metabolic breakdown product of purine nucleotides
36	Creatinine	Cr	Waste product that comes from the wear and tear on muscles of the body
37	Tocopherol	VIT E	Fat-soluble vitamin functions as an antioxidant
38	BCL2 Associated X protein	Bax	The protein forms a heterodimer with BCL2 and functions as an apoptotic activator

39	B-cell lymphoma 2	Bcl2	Regulatory protein that regulate apoptotic cell death by either inhibiting anti-apoptotic or inducing pro-apoptotic proteins
40	Total triglycerides	TG	Type of fat found in blood and also stored in fat cells, high levels may be an indication of cardiovascular disease
41	Total protein	TP	Total amount of protein in serum, it is often elevated in pathologic conditions like infection, inflammation,etc

Table 2

3.2 Biochemical Parameter

The heart was removed from each animal and its fresh weight was recorded. The isolated hearts were kept at −80 ◦C and subsequently homogenized in cold potassium phosphate buffer (0.05 M, pH 7.4). The homogenates were centrifuged at 5000 rpm for 10min at 4^0C.

1	Glutathione S Transferase	GST	Catalyze the conjugation of the reduced form of glutathione to xenobiotic substrate for detoxification
2	Glutathione disulfide	GSSG	Derived from 2 glutathione molecules, it is reduced to GSH functioning as an antioxidant system
3	Glutathione reductase	GR	Enzyme responsible for maintaining the supply of reduced glutathione
4	Peroxidase	POD	Group of enzymes that catalyze the oxidation of substrate
5	γ-Glutamyl transpeptidase	γ-GT	Catalyzes the removal of glutamyl groups of aromatic amines into its constituent amino acids
6	Glutathione peroxidase	GPx	Cytosolic enzyme that catalyzes the reduction of hydrogen peroxide to water and oxygen
7	Sodium-potassium Adenosine Triphosphatase	Na^+ K^+ ATPase	Membrane bound enzyme helps maintain resting potential, affects transport, and regulates cellular volume
8	Magnesium Adenosine Triphosphatase	Mg^{2+} ATPase	Transmembrane enzyme, responsible for sequestration of calcium in the lumen of sarcoplasmic reticulum in muscle against a considerable concentration gradient
9	Calcium Adenosine Triphosphatase	Ca^{2+} ATPase	Enzyme that transfers calcium after a muscle has contracted
10	Reduced Glutathione	GSH	Key component of the antioxidant system helps protect the body from free radicals
11	Malondialdehyde	MDA	One of the final products of PUFA peroxidation in the cells. An increase in free radicals causes overproduction of MDA
12	Superoxide dismutase	SOD	Enzyme catalysis of dismutation of superoxide radical into oxygen and hydrogen peroxide
13	Catalase	CAT	Enzyme responsible for the breakdown of hydrogen peroxide into oxygen and water
14	Tumor Necrosis Factor-alpha	TNF-α	Proinflammatory cytokine that plays a critical role in cell proliferation, differentiation, and apoptosis
15	nitric oxide	NO	it is a Free radical, that functions to increase blood flow and lower BP
16	Monocyte chemoattractant protein-1	MCP 1	Chemokine that regulates migration and infiltration of monocytes /macrophages. It is highly expressed in atherosclerotic plaques
17	Galectin 3	Gal-3	It is an inflammatory β-galactoside binding lectin secreted by activated macrophages that when bound to the matrix, exerts matricellular functions
18	Collagen 1	COL1A1	Most abundant protein that forms a structural and mechanical scaffold
19	Myeloperoxidase	MPO	Heme containing enzyme expressed mainly in neutrophils, monocytes, etc. Catalyzes the formation of ROS for antimicrobial property
20	Calcium	Ca^{2+}	Important role in blood clotting, contraction, heart rhythm, nerve functions,etc
21	Potassium	K^+	Helps maintain normal levels of fluid inside our cells, also helps muscles to contract, and maintains BP
22	Magnesium	Mg^{2+}	Supports muscle and nerve function, chronically low levels can increase the risk of high BP, heart disease, type 2 DM, osteoporosis
23	Sodium	Na^+	BP and blood volume homeostasis, also for conducting nerve

			impulses, contracting and relaxing muscles

Table 3

3.3 Immunohistochemistry

Four mm thick sections were deparaffinized, rehydrated, and endogenous peroxidase activity was blocked with H_2O_2 in methanol. Sections were pre-treated in citrate buffer (pH 6.0). Sections were incubated at room temperature with rabbit polyclonal antibodies specific to the rat targets. Sections were incubated with biotinylated goat anti-polyvalent, then with streptavidin peroxidase and finally with diaminobenzidine plus chromogen. Slides were counterstained with hematoxylin, visualized under a light microscope and the extent of cell immunopositivity was assessed by using a semi-quantitative analysis.

1	Inducible nitric oxide synthase	iNOS	Mediator of unspecific host defense inhibits t-cell activity
2	Nuclear factor kappa B	NF-Kb	Protein transcription factor considered as a regulator of innate immunity
3	Caspase-3	CPP-32	Frequently activated death protease, catalyzing the specific cleavage of many key cellular proteins mediating apoptosis

4. CARDIOPROTECTIVE ACTIVITIES OF PLANT SPECIES AGAINST DRUGS INDUCED CARDIOTOXICITY

Table 4

Description of experimental studies performedshowing cardioprotective effects and outcomes which are arranged in chronological order (2010 – Feb 2022)

SL NO	AUTHOR NAME	PLANT NAME	MODEL USED	EVALUATION PARAMETERS	OUTCOMES AND CONCLUSION
1	Mohammad HassanpourFard et al., 2010[16]	*Punica granatum* Whole fruit extract of Pomegranate (WFEP)	Doxorubicin	CK-MB, LDH, AST, SOD, GSH, MDA, and ECG	WFEP has the ability to reduce oxidative stress and significantly decreased QT interval, no ST-segment changes, and increased heart rate
2	Patel et al., 2010[17]	*Syzygium cumini* (Hydroalcoholic seed extract)	Doxorubicin	CK, LDH, AST, ALT, GSH, GST, GPx, CAT, SOD, GR, HDL, LDL and TG	The extract significantly reversed pathological alterations caused by DOX through its antioxidant effect.
3	Ahmed A. Elberry et al., 2010[18]	*Vaccinium macrocarpon* (Cranberry extract-CRAN)	Doxorubicin	cTnI, CK-MB, CK, LDH, GSH, GSSG, COX-2, MDA, CAT, SOD, GPx and GR	CRAN protects against DOX-induced cardiotoxicity in rats as evidenced by improved mortality and effusion scores, mitigation of ECG abnormalities
4	Ponniah Senthil Murugan et al., 2011[19]	*Acalypha indica* (Methanolic extract)	Isoprenaline	cTnT, CK-MB, LDH, HsCRP, MDA, CAT, and SOD	Methanolic extract possesses potent cardioprotective activity, further studies are needed to identify the active compounds.
5	L. Vibha et al., 2011[20]	*Allium sativum* (Paste suspension in distilled water)	Isoprenaline	CK-MB, LDH, SOD, CAT, and MDA	Medicinal ginger possesses cardioprotective activity against ISO induced myocardial necrosis, further studies need to be conducted to evaluate the active principle.
6	Sita Sharan Patel et al., 2011[21]	*Bombax ceiba* (Aqueous flower extract)	Doxorubicin	LDH, ALT, MDA, TP, GSH, GPx, SOD and CAT	BC showed cardioprotective effect against DOX-induced MI and it may be due to its antioxidant effect.
7	Shreesh Ojha et al., 2011[22]	*Emblica officinalis* (Hydroalcoholic extract)	Isoprenaline	CK-MB, LDH, MDA, SOD, CAT, GSH, GPx, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, and heart rate	Extract improves biochemical defense and contractile function along with histopathological salvage of the myocardium and delays the progression of myocardial ischemia.
8	Shreesh Ojha et al., 2011[23]	*Commiphoramukul* (Hydroalcoholic	Isoprenaline	CK-MB, LDH, MDA, SOD, CAT, GSH and GPx	Protective effects of extract against ISO-induced MI are related to its effects on

		extract of guggul)			counteraction of free radicals and membrane-stabilizing action.
9	T.Vijay et al., 2011[24]	*Gmelina arborea* (Ethanolic extract)	Doxorubicin	CK, ALT, AST, LDH, LDL, HDL, VLDL, LDH, GSH, GPx, MDA, CAT, GR and SOD	The identification of molecules with cardioprotective potential from this ethanol extract of GA may provide new directions for the identification of cardioprotectives
10	Upaganlawar A et al., 2011[25]	*Lagenaria siceraria* (Semi-ripe fruit juice)	Isoprenaline	LDH	Fruit juice showed protective effect on ISO-induced MI, effects might be due to the presence of polyphenolic compounds.
11	Roya Mehdizadeh et al., 2012[26]	*Crocus sativus* (Saffron aqueous extract)	Isoprenaline	CK-MB, CK, LDH, and MDA	Pretreatment with saffron and safranal reduced histopathological changes in heart tissue and decreased CK-MB and LDH activities in serum via reduction of oxidative stress.
12	S. Madhumitha et al., 2012[27]	*Morus alba* (Methanolic leaf extract)	Isoprenaline	CK, LDH, SOD, CAT, GSH, GPx and MDA	The extract is effective in reducing the extent of myocardial damage and significantly counteracted the oxidative stress
13	Sarah Len O. Rosales et al., 2013[28]	*Bambusablumeana* (Ethanolic leaf crude extract)	Isoprenaline	CK-MB, LDH, and AST	Leaf extract exerts dose dependent cardioprotective action by slackening inflammation and cardiac biomarkers
14	Bandari Uma Mahesh et al., 2013[29]	*Boswellia ovalifoliolata* ‘ (Ethanolic stem-bark extract)	Doxorubicin	CK-MB, LDH, AST, ALT, CAT, SOD, MDA, GSH, ROS, and ECG	Ethanolic extracts of BO hhavea significant therapeutic benefit when administered along with DOX therapy by attenuating oxidative stress and lipid peroxidation.
15	Amr A. Fouad et al., 2013[30]	*Cannabis sativa* (Cannabidiol)	Doxorubicin	TNF-α, NF-kB, iNOS, NO, CPP-32, Ca^{2+},Selenium, Zinc,and GSH	Cannabidiol treatment significantly ameliorated DOX-induced cardiotoxicity due to its potent antioxidant and anti-inflammatory effect.
16	Herwandhani Putri et al., 2013[31]	*Citrus hystrix* (Citrus hystrix peel Ethanolic extract-ChEE)	Doxorubicin	AST and ALT	ChEE could reside most parts of its free radical scavenger activity and it can be used clinically to improve the therapeutic benefits of DOX
17	Razieh Afshar Moghaddam et al., 2013[32]	*Camellia sinensis* (Ethanolic extract of leaves)	Isoprenaline	LDH, ALT, GSH, MDA, SOD, and CAT	Extract showed dose dependent cardioprotection with significant changes in the myocardial muscle fibers and inflammatory cells.
18	S. Palani et al., 2013[33]	*Flacourtia indica* (Ethanolic leaf extract)	Doxorubicin	CK, LDH, LDL, AST, ALT, HDL, VLDL, SOD, MDA, CAT, GSH and GPx	Ethanolic extract possesses marked cardioprotective activity demonstrated by changes in the serum marker enzyme. Further studies will be carried out to find the compound that is responsible for activity.

19	V.dhanarangeshkumar et al., 2013[34]	*Garcinia indica* (Ethanolic fruit extract)	Isoprenaline	CK-MB, CK, LDH, AST, ALT, Na^+ K^+ ATPase, Mg^{2+} ATPase and Ca^{2+} ATPase	Pre-treatment with extract providescardioprotection by inhibiting the formation of free radicals and also improved the status of enzymatic antioxidants
20	MahsaZareiet al., 2013[35]	*Hemidesmus indicus* (Methanolic root extract-HiRe)	Doxorubicin	CK, LDH, AST, ALT, SOD, CAT, GPx, GSH and MDA	HiRe can be considered as a good chemo protector against Dox-induced cardiotoxicity by boosting the antioxidant capacity of the heart. So, this will become a ray of hope for cancer patients.
21	Sudeep Shah et al., 2013[36]	*Hypericum hircinum*	Doxorubicin	CK, LDH, ALT, GSH, MDA, SOD and ECG	Plant extract has the potential to prevent the cardiotoxic effects induced by DOX.
22	Adi K at al., 2013[37]	*Parkia biglobosa* (Hydroalcoholic stem bark extract)	Isoprenaline	CK, LDH, LDL, HDL, VLDL, TC, TG and MDA	Extract ameliorated positively biochemical alterations, prevented oxidative stress and histological and morphological changes induced by ISO may be due to its antioxidant and antihyperlipidemic activities
23	Mukesh Nandave et al., 2013[38]	*Picrorhizakurroa* (Methanolic root extract)	Isoprenaline	CK-MB, LDH, SOD, CAT, GSH, GPx, and MDA	The study demonstrates the cardioprotective effect of extract against ISO induced MI and validates the traditional claim. Further studies need to be done for its clinical use in IHD
24	Nishith Ranjan Barman et al., 2013[39]	*Urtica parviflora* (Ethanolic extract)	Isoprenaline	ALT, AST, ALP, LDL, HDL, TG, TC, CAT and GSH	U. parviflora prevented the ISO-induced cardiotoxicity by boosting the endogenous antioxidant activity. It could be due to the antioxidant activity and restoration of myocardial biomarkers.
25	Sunanda Panda et al., 2013[40]	*Vinca rosea* (vincristine)	Isoprenaline	cTnT, CK-MB, AST, LDH, Na^+ K^+ ATPase, Mg^{2+} ATPase, Ca^{2+} ATPase and ECG	Treatment with vincristine at moderate dose provides cardioprotection, through the enhancement of antioxidant defense mechanism.
26	V. PAVLOVA et al., 2014[41]	*Aronia melanocarpa* (Black chokeberry)	Doxorubicin	GSH	Aronia melanocarpa total extract had ameliorating effect on DOX-induced cardiotoxicity via mechanisms related to the reduction of cellular oxidative stress.
27	Yuan Cao et al., 2014[42]	*Astragalus membranaceus*	Doxorubicin	ECG, TUNEL, DNA laddering, and Western blotting	APS suppressed oxidative stress and apoptosis, ameliorating doxorubicin-mediated cardiotoxicity by regulating the PI3k/Akt and p38MAPK pathways.
28	Ahmed A. Zaki et al., 2014[43]	*Boswellia carteri* (Olibanum methanol extract)	Isoprenaline	CK-MB, ALT, LDH and MDA	Methanolic extract exhibited a cardioprotective effect, particularly on administering high doses, determined both biochemically and histopathologically

29	Masood S. Khan et al., 2014[44]	*Bombyx mori* (Aqueous extract)	Doxorubicin	CK-MB, LDH, MDA, CPP-32, TNF-α, IL-6, and SOD	Aqueous extract of BM has cardioprotective potential, this may be due to high content of amino acids and flavonoids
30	B. Santhosh Kumar et al., 2014[45]	*Buchananiaaxillaris* (Ethanolic leaves extract)	Doxorubicin	CK, LDH, and AST	Ethanolic leaf extract attenuated the DOX-induced cardiotoxicity further experimental studies are needed to isolate the active/lead biomolecules.
31	Farogh Ahsan et al., 2014[46]	*Coleus forskohlii* (Ethanolic root extract)	Isoprenaline	cTnI, CK-MB, CK, LDH, AST, and ALT	Ethanolic extract attenuates ISO-induced MI. The cardioprotective activity is probably related to its ability to strengthen the myocardial membrane by its membrane stabilizing action
32	Abdullah S. Shatoor et al., 2014[47]	*Crataegus aronia* (Aqueous extract)	Doxorubicin	CK-MB, LDH, GSH, GPx, GR, SOD, MDA and CAT	Aqueous extract following DOX treatment ameliorated damage to cardiac tissue by modulating the pathways that trigger cardiotoxicity. Additional animal and human trials are needed to confirm the active ingredient
33	Abi Beaulah G et al., 2014[48]	*Croton sparciflorus* (Methanolic extract)	Isoprenaline	CK-MB, LDH, AST, ALT, TC, TG, HDL, LDL, SOD, CAT and MDA	The plant extract has the potential to inhibit thcardiotoxicic effects induced by ISO and possesses a significant medicinal value in the prophylactic treatment of MI
34	K.Sobhana et al., 2014[49]	*Pandanus odoratissimus* (Hydroalcoholic leaves extract)	Isoprenaline	CK-MB, LDH, CAT, SOD, GSH, and MDA	Hydroalcoholic extract showed significant dose dependent cardioprotective activity; flavonoids may be responsible for this effect
35	Hardik Savsani et al., 2014[50]	*Premna mucronate* (Methanolic extract)	Isoprenaline	CK-MB, LDH, α-HBDH, Na^+ K^+ ATPase, Mg^{2+} ATPase, Ca^{2+} ATPase, Na^+, K^+, Ca^{2+}, Mg^{2+}, MDA, GSH, SOD, CAT and ECG	Methanolic extract showed dose dependent cardioprotection against ISO induced MI by altering changes in ions, normalized ECG pattern,andhemodynamicc changes.
36	Kyu Hee Lim et al., 2014[51]	*Panax ginseng*	Isoprenaline	CK-MB, LDH, SOD, CAT, GSH, MDA, GPx and ECG	Pretreatment with ginseng significantly reduced serum biomarkers, inhibiting neutrophil infiltration in the myocardium, this effect may be due to its antioxidant effect.
37	Heba A. Aniss et al., 2014[52]	*Salsola kali* (Aqueous extract)	Doxorubicin	CK, LDH, AST, ALT, MDA, NO, GSH, GPx, MDA, GST and CAT	S. kali aqueous extract had a potential antioxidant activity which ameliorated ADR-induced cardiotoxicity
38	Jay Rabadia et al., 2014[53]	*Syzygium Aromaticum* (Methanolic flower extract)	Isoprenaline	CK-MB, CK, LDH, AST, ALT, GSH, GST, GPx, MDA, CAT and SOD	S.aromaticum modulated most of the biochemical analysis and tissue enzyme analysis Further isolation, characterization, and

					purification of the active constituentsare required.
39	Ganesh Chandra Jagetia et al., 2015[54]	*Aegle Marmelos*	Doxorubicin	CK-MB, LDH, AST, ALT, GSH, MDA, CAT, GPx and ECG	AME has been reported to stabilize cardiac cell membranes and preserve their integrity by regulating cardiac enzyme release
40	A. Gnanapragasam et al.., 2015[55]	*Centella asiatica* (Aqueous extract)	Doxorubicin	CK, LDH, ALT, GPT, SOD, CAT, GPx and GST	Extract enhances myocardial antioxidants and significantly prevents the heart fromDOX-inducedd oxidative stress. Further studies are in progress to elucidate the exact mechanism.
41	Abba PacômeObouayeba et al., 2015[56]	*Hibiscus sabdariffa* (Aqueous flower extract)	Doxorubicin	CK-MB, LDH, AST, and ALT	Aqueous extract of H. sabdariffa red petals helps to protect the heart, and the reduction of inflammation
42	Honi Yalu et al., 2015[57]	*Kigelia Africana* (Methanolic leaves extract)	Isoprenaline	AST, ALT, ALP, LDH, TC, TG, LDL, HDL, MDA, GSH, CAT and SOD	Leaf extract showed dose dependent cardioprotection, prevented alterations in biomarkers, and showed normal myofibrillar structures
43	Zhao-Hua Geng et al., 2015[58]	*Salvia miltiorrhiza* (Polysaccharide-SMP)	Isoprenaline	CK-MB, LDH, AST, ALT, ALP, LDL, HDL, SOD, CAT, GSH, GPx and MDA	SMP was safe and highly effective in preventing the ISO-induced MI in rats, which was at least by virtue of its antioxidant and antihyperlipidemic activities
44	Babatunji Emmanuel Oyinloye et al., 2015[59]	*Sesamum indicum* (Aqueous extract-SI)	Cadmium	AST, ALT, ALP, TC, TG, LDL, HDL, GSH, GST, GPx, SOD, CAT and MDA	SI possesses antioxidant and cardioprotective potential in a dose-dependent manner. SI has potential in the novel treatment of cardiotoxicity and management of oxidative stress
45	Santosh K Shukla et al., 2015[60]	*Terminalia arjuna* (Hydroalcoholic bark extract-HETA)	Isoprenaline	cTnI, CK-MB, LDH, ALT, GSH, SOD, and MDA	HETA pretreatment exerts better antioxidant and anti-apoptotic which further strengthens the cardioprotective activity
46	Geeta B. Kharadi et al., 2016 [61]	*Allium cepa* (Aqueous extract)	Isoprenaline	cTnI, CK-MB, AST, LDH, SOD, MDA, and ECG	A. cepa at low dose was found to be cardioprotective against myocardial injury while at high dose did not show a significant effect. So, we presume that it might be effective within a certain dose range only
47	Mona A. M. Ghoneim et al., 2016[62]	*Adansonia digitata* (Total protein extract)	Isoprenaline	CK-MB, LDH, AST, MCP-1, MPO, IL-1β, GSH, GPx, Ca^{2+}, K^{+}, Mg^{2+}, COL1A1, Gal-3, and serum corticosterone	A. digitata exerts significant cardioprotective effects against ISO-induced MI. This protective effect could be due to antioxidant defense system of GSH, and GPx.
48	R. Varadharajan et al., 2016[63]	*Cucumis callosus* (Ethanolic extract)	Doxorubicin	AST, ALT, ALP, TC, TG, MDA, GSH, GPx, GST, SOD and CAT	Extract prevented the DOX-induced myocardial toxicity by boosting the endogenous antioxidant activity. The effect might also be due to the lipid-lowering effect
49	Sadiya khwaja et al.,	*Cyperus rotundus*	Isoprenaline	CK-MB, LDH, ALT,	Extract showed significant

	2016[64]	(Ethanolic extract)		and AST	dose dependent cardioprotection and it is attributed to the presence of flavonoids
50	JaganathanAnitha et al., 2016[65]	*Eudriluseugeniae* (Earthworm powder-EWP)	Isoprenaline	LDH, HDL, VLDL, LDL, TG and TC	EWP treatment group tends to ameliorate the changes mediated by ISO without any adverse side effects. The isolation of the pure compound responsible for these stabilizing properties is now in progress.
51	Ravi Mundugaru et al., 2016 [66]	*Garcinia pedunculata* (Aqueous fruit extract)	Isoprenaline	CK-MB, AST, ALT, ALP, and HsCRP	The extract protected experimentally induced MI, revealed by the amelioration of histological changes, and biochemical and inflammatory markers of cardiac tissue damage.
52	Karthikeyan k.m.r et al., 2016[67]	*Helicteresisora* (Ethanolic extract of bark)	Isoprenaline	cTnI, CK-MB, LDH, HDL, LDL, VLDL, ALT, AST, BUN, Cr, MDA, SOD, GSH, TC and ECG	High dose extract produces significant cardioprotection against ISO induced MI. Further characterization of the active constituents would be necessary to elucidate the exact mechanism of action
53	Tayyaba Afsar et al., 2017[68]	*Acacia hydaspica* (bark, twigs, and leaves extract)	Doxorubicin	CK-MB, CK, AST and LDH, CAT, POD, SOD, QR, GSH, GST, GSR, GPx, γ-GT and MDA	AHE may be beneficial for DOX-induced cardiotoxicity by ameliorating oxidative stress, basic research needs to be done in a relevant model to explicate the mechanism
54	Mohamed M. Abdel-Daim et al., 2017[69]	*Allium sativum*	Doxorubicin	CK-MB, LDH, TNF-α, IL-1β, 8-OHdG, CAT, MDA, NO, GSH, GPx and SOD	Pretreatment with allicin significantly ameliorated the biochemical and histological changes, induced by DOX
55	FulyaBenzer et al., 2017[70]	*Curcuma longa* (Curcumin)	Doxorubicin	cTnI, CK-MB, LDH, NF-kB, TNF-α, and IL-1β, iNOS, CAT, GPx, GSH, MDA, and SOD	Curcumin attenuates DOX-associated cardiotoxicity by reducing ROS
56	YUAN Yan et al., 2017[71]	*Ilex cornuta* (Hydroalcoholic root extract)	Isoprenaline and Pituitrin	CK, LDH, SOD, MDA, and GSH	ICR may have cardioprotective effects achieved by its antioxidant and anti-apoptosis activities, so it may be a potential natural therapeutic source for the treatment of cerebral ischemia
59	Kamrun Nahar et al., 2018[72]	*Amaranthus tricolor* (Red spinach leaf extract)	Isoprenaline	CK-MB, CAT, LDL, HDL, MPO, NO, AST, ALT, ROS, TNF-α, IL-1β, iNOS, NF-kb, GSH, MDA and SOD	A. tricolor extract is effective in ISO-induced MI, this could be associated with the reduction of the extent of myocardial damage caused by oxidative stress and attenuation of inflammatory cells infiltration.
60	Radwa A. Eladwy et al., 2018[73]	*Vaccinium angustifolium* (Blue berry leaf extract)	Isoprenaline	cTnI, CK-MB, LDH, AST, GSH, MDA, CAT, IL-6, TNF-α, NK-kb, COX-2, TGF-β, and ECG	BB extract alleviates the ISO-induced cardiotoxicity as evidenced by lowering myocardial injury markers and preventing ECG abnormalities and

					histopathological changes
61	Rakam Gopi Krishna et al., 2018[74]	*Bougainvillea glabra* (Methanolic whole plant extract)	Isoprenaline	CK-MB, ALT, AST, TG, TC, HDL, LDL, VLDL, TP, CAT, SOD, GSH, GPx and MDA	The cardioprotective effect of plant extract is probably related to a counteraction of free radicals by its antioxidant property. Histopathological findings further confirmed the cardiac protective effect.
62	Nahar S te al., 2018[75]	*Curcuma Longa*	Isoprenaline	AST and LDH	Curcuma longa has cardioprotective effect on ISO induced myocardial injury, so it is acceptable as a daily source of naturalantioxidantst.
63	BhupalamPradeepkumar et al., 2018[76]	*GymnemaSylvestre* (Flavanoid fraction from leaf extract)	Doxorubicin	CK-MB, LDH, AST, TC, TG, MDA, UA, Ca^{2+}, NO, SOD, CAT, Na^{+} K^{+} ATPase, Mg^{2+} ATPase, Ca^{2+} ATPase, GSH, MDA	Pre-treatment of rats with the flavonoid fraction of GymnemaSylvestre significantly ameliorated the toxic insult perpetrated by dox
64	Hyo-Suk Ahn et al., 2018[77]	*Ecklonia cava* (Methanolic extract from brown algae)	Doxorubicin	CK-MB, LDH, AST, ALT, TC, TG, HDL, LDL, CAT, SOD and ECG	EC was safe and cardioprotective against ISO-induced cardiotoxicity in a dose-dependent manner with the evidence based on biochemical results and histopathological findings
65	Orelien Sylvain MtopiBopda et al. 2018[78]	*Kalanchoe pinnata* (Aqueous leaf extract)	Isoprenaline	CK-MB, ALT, TC, and TG	The extract decreased cardiovascular biomarkers levels in ISO-administered rats while protecting the heart from injury. Therefore, the extract might have cardioprotective properties, if administered at 100-200mg/kg/day
66	Farzana Akther Sumi et al., 2019[79]	*Aloe vera* (Hydroalcoholic gel extract)	Isoprenaline	CK-MB, ALT, ALP, AST, SOD, CAT, GSH, and MDA	Aloe vera gel showed cardioprotective activity, this may be attributed to the restoration of antioxidant enzymes and decreased lipid peroxidation of the heart.
67	Ekram Nemr Abd Al Haleem et al., 2019[80]	*Casuarina suberosa* (leaf extract)	Isoprenaline	cTn, CK-MB, LDH, AST, ALT, MPO, CAT, GSH, SOD, NO, MDA, GST, and ECG	leaves extract reduces ISO-induced cardiotoxicity, prevention myocardial necrosis and accompanying oxidative stress
68	Agnel Arul John Nayagam et al., 2019[81]	*Caesalpinia bonducella* (Aqueous plant extract)	Doxorubicin	cTnT, CK-MB, CK, LDH, Na^{+} K^{+} ATPase, Mg^{2+}ATPase, Ca^{2+} ATPase, HDL, LDL, VLDL, TP, DNA, RNA, TC, TG	Caesalpinia bonducella L. protects cardiac muscle and helps in maintaining the myocardial cell membrane integrity and function thereby protecting the cells from rupture and preventing leakage of the cardiac markers and lipids
69	Maha Abu Gazia et al., 2019[82]	*Elettaria cardamomum* (Aqueous extract)	Doxorubicin	cTnT, LDH, CK, NO, MDA, SOD, CAT, GPx, CAS-3, and NF-Kb	CAR extract ameliorated the toxic effect of DOX by reducing structural disruptions and functional disturbances via lowering serum parameters

70	Samer Tariq Jasim et al., 2019[83]	*Gingko Biloba*	Doxorubicin	cTnI, TNF-α, CPP-32, BNP, MDA, and GSH	Ginkgo Biloba was found to have a significant cardioprotective effect through attenuation of oxidative stress DOX-induced cardiotoxicity, this may be due to flavonoids
71	C. Sumanjali et al., 2019[84]	*Pulicariawightania* (Ethanolic leaf extract)	Isoprenaline	CK-MB, LDH, AST, ALT, ALP, TC, TG, HDL, LDL and VLDL	Treating with extract alters cardiac biomarkers and helps to treat coronary heart disease, which may be due to the antioxidant effect of flavonoids
72	Zhenhuang Shen et al., 2019[85]	*Schisandra chinensis* (Bee pollen extract-SCBPE)	Isoprenaline	Bc12, Bax, HO-1, Nrf-2, AST, LDH, CK, SOD, GPx and CAT	SCBPE exert an antioxidative and cardioprotective effect. The study provides a scientific basis for functional food for the prevention of MI
73	Salma A. El-Marasy et al., 2020[86]	*Thymus vulgaris* (Thymol)	Adrenaline	CK, GSH, MDA, LDH, AST, NF-kB, IL-1β, CPP-32, Bcl-2, and ECG	Thymol possessed cardioprotective effect against adrenaline-induced MI by ameliorating cardiac tissue biomarkers, attenuating ECG changes, improving histopathological changes resulting from oxidative stress, inflammation, and apoptosis
74	Priya Bisen et al., 2020[87]	*Amaranthus cruentus* (Ethanolic leaf extract)	Isoprenaline	AST, ALP, ALT, LDL, VLDL, HDL and TC	The outcomes of the present study revealed a cardio-protective effect of Amaranthus cruentus extract. There was an increase in the overall integrity of targets studied, mechanism need to be established
75	Hassan N. Althurwi et al., 2020[88]	*Cymbopogon Proximus* (Hydrodistilled essential oil)	Isoprenaline	ANP, BNP, β-MHC, P1NP and P3NP	C. Proximus showed cardioprotective against ISO induced cardiac hypertrophy and fibrosis. The correlation between pure components of the essential oil extract and the observed effect needs to be done
76	MbidaHacheked et al., 2020[89]	*Datura metel* (Aqueous seed extract-AESDM)	Doxorubicin	AST, ALT, TC, TG, MDA, SOD, CAT, GSH, HDL and LDL	AESDM preventsDOX-induced cardiotoxicity, antioxidant and hypolipidemic properties may be due to alkaloids, flavonoids.
79	A. O. Fajobi et al., 2020[90]	*Pterocarpus mildbraedii* (Methanolic leaf extract)	Isoprenaline	cTnT, CK-MB, LDH, TP, TG, TC, LDL, HDL, VLDL, GSH, SOD, CAT, heart and plasma (VIT C and VIT E), ALA, GSH, GPx	The study demonstrates the protective effect of P.mildbraedii. This might be due to the presence of vital constituents which have been reported to possess antioxidant and hypocholesterolemic activities
80	Rahul Chaudhary et al., 2020[91]	*Terminalia bellirica* (Methanolic extract-METB)	Doxorubicin and Isoprenaline	cTnI, cTnT, CK-MB, MDA, CK, SOD, CAT, GSH, ALP, AST, ALT, UA, TC,	METB showed dose dependent cardioprotection. The myocardial stabilizing effects are beneficial on

				TG, HDL, LDL, and VLDL	cardiac health in patients to avoid/minimize the risk of cardiotoxicity
81	FayzaTawfiekAbdl Aziz et al., 2021[92]	*Bauhinia madagascariensis* (Methanolic extract) *Bauhinia purpurea* (Methanolic extract)	Adrenaline	CK-MB, LDH, AST, ALT, ACE, TNF-α, MMP-9, iNOS, NO, GSH, MDA, and ECG	Both extracts possessed a potent protective activity against adrenaline-induced cardiotoxicity via improving cardiac function through its anti-oxidant, anti-inflammatory effects
82	EneteUchenna et al., 2021[93]	*Jatropha tanjorensis* (Methanolic leaf extract)	Isoprenaline	cTnI, CK-MB, LDH, HsCRP, MDA, SOD, GSH, GPx, and CAT	To some extent, extractpossessess mild cardioprotective potency at a certain dose range but could not serve as a potential agent for the prevention of cardiotoxicity. The result of this study revealed the need for proper dosing of crude drug
83	Aminu Lailaba Abubakar et al., 2021[94]	*Sclerocaryabirrea* (Methanolic Stem bark extract)	Doxorubicin	cTn, CK, AST, MYO, MDA, SOD, CAT, and ECG	S. birrea effectively prevented tissue damage by decreasing the oxidative stress through antioxidant therapy making it a suitable candidate to ameliorate MI
84	Ioana Corina Bocsan et al., 2021[95]	*Nigella sativa* (NSO) *Vitis vinifera* (GSO)	Isoprenaline	cTnT, CK-MB, AST, ALT, IL-1β, IL-6, TNF-α, IL-10 and ECG	NSO and GSO partially prevented ECG alterations and the modification of biological and inflammatory parameters. Both compounds were shown to have good potential for future treatment in CVDs
85	HodaQuaisul et al., 2021[96]	*Withaniacoagulans* (coagulin)	Isoprenaline	cTnI, CK-MB, AST, ALT, TG, TC, LDH, HDL, LDL, GSH, GPx, GR, SOD, CAT and MDA	Coagulin improved myocardial histoarchitecture against ISO-induced MI, the present study strongly suggests that multiple mechanisms may be responsible for the cardioprotective effect
86	M. Santosh Kumar et al., 2022[97]	*Acorus calamus* (Ethanolic extract)	Doxorubicin	CK-MB, LDH, CK, Na^+ K^+ ATPase, Mg^{2+} ATPase, Ca^{2+} ATPase, TC, TG, HDL, GSH, MDA, SOD, CAT and ECG	The study suggests that AC protects from CVDs, improved cardiac injury markers, maintained the BP, and re-establishment antioxidant status are seen. Further molecular level of investigation is to be done
87	Dalia I. Hamdan et al., 2022[98]	*Morus macroura* (Dichloromethane leaf extract)	Isoprenaline	CK-MB, LDH, and SOD	Extract showed cardioprotective and antidepressive properties against ISO-induced post-MI depression as they persuade cardioprotection by decreasing myocardial enzymes and safeguarding the cardiac muscle histology

5. CONCLUSION

This comprehensive evaluation aids in identifying the cardioprotective potential of various extracts by examining their effects on various in-vitro and in-vivo parameters in the presence of medications that cause cardiotoxicity. The researchers propose anti-

oxidant, anti-apoptotic, and anti-inflammatory properties, as well as ion channel regulation, metal chelation, and activation/inhibition of cellular or non-cellular enzymes as possible mechanism. However, because the current evidence is restricted to preclinical trials, identification of the individual phytochemical responsible, and a poor pharmacokinetic profile in humans, hence derivatives of phytochemicals should be taken into the picture to improve their profile.

In contrast, given natural products' multitarget and multicomponent action strategies, the extract could be a unique supplementary way to improve the therapeutic potential in cardiomyopathy patients by modulating the pathogenic process of cardiomyocyte cell death and increasing heart function. In addition, only a few of the plant extracts and formulations researched for their therapeutic and preventive effects in experimental cardiotoxicity models have been studied in clinical trials.

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