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AMELIORATION OF CARDIOTOXICITY INDUCED BY DOXORUBICIN THROUGH CARDIOPROTECTIVE HERBAL DRUGS

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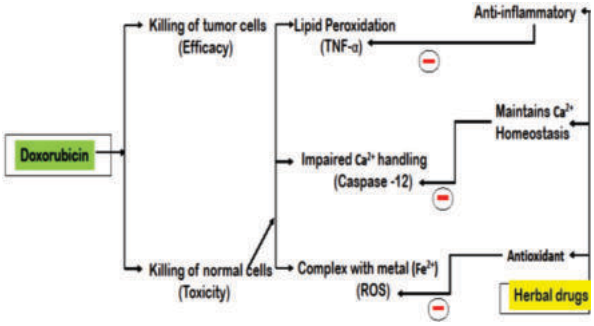
ABSTRACT

Background: Anthracycline (doxorubicin) most widely used chemotherapeutic agent for various malignancies like breast cancer, lung cancer, sarcoma & leukemia due to its excellent efficacy but its use is limited due to cardiotoxicity. Cardiotoxicity of doxorubicin has another mechanism of its antineoplastic effects. Cardiotoxicity includes electrophysiological changes like arrhythmia, QT prolongation, pericarditis, myocarditis, contractile dysfunction, decrease left ventricular ejection fraction & heart failure. **Objective:** Herbal drugs can mitigate cardiotoxicity by using cardio protective natural (Herbal) drugs with doxorubicin. Doxorubicin has antitumor activity by inhibiting DNA replication & RNA transcription, but doxorubicin has cumulative dose effect, it accumulates in cardiolipin of internal mitochondrial membrane and make complex with metals (Fe, Zn & Cr) and release free radicals and increase malondialdehyde(MDA), TNF-α and decrease glutathione peroxidase(GSP), catalase. Free radicals are responsible for cardiotoxicity. Hence herbal drugs act against doxorubicin-induced cardiotoxicity by the mechanism of antioxidant action, calcium ions regulation & inhibition of free radical's formation or reactive oxygen species and decrease malondialdehyde, TNF-α and increase glutathione peroxidase, catalase. Therefore, these herbal (Rutin, Ginkgolide-B, Crocin, Naringin, Thymol, Mangiferin) are used as cardioprotective agents. **Method:** We discussed in this review, the properties of natural herbal drugs which extracted from plant species. These herbal drugs have antioxidant action, calcium ions regulation & inhibition of free radical's formation in cardiotoxicity induced by chemotherapeutic agent Doxorubicin models. Data extracted for review from MEDLINE/PUBMED, Google Scholar and SCOPUS. Data of Extracted compounds from plant species used in this review, that have been tested using in vivo and in vitro doxorubicin models and published between 01/01 2005 and 01/01/2024. **Results:** Herbal Drugs such as resveratrol, Grape polyphenols, isorhamnetin, Curcumin, Garlic, Ganoderma lucidium, Rutin, Gingolide-B Crocin, Naringin, Mangiferin and ellagic acid Compounds that have been reported to have antioxidant action, calcium ions regulation & inhibition of free radical's formation activity with defined mechanisms (like, antioxidant, anti-inflammatory, anti-apoptotic and mitochondrial- protection). **Conclusion:** Based on Preclinical studies data, can concluded that herbal drugs (Mangiferin, Rutin, Crocin & Ginkgolide-B) causes regulation of intracellular calcium homeostasis & have antioxidant potential leads to reduced DOX-induced intrinsic apoptotic pathways activation and the subsequent heart damage. However, their clinical application is limited by insufficient human trials, bioavailability challenges, and variability in herbal preparations.



KEYWORDS : Doxorubicin, Cardiotoxicity, Cardiolipin, ROS, Cardioprotective, Caspase pathway, Herbal Drugs.

INTRODUCTION:

Anthracycline is an antineoplastic agent, most extensively used in the treatment of different types of malignancies for example Solid tumor, Leukemia, Carcinoma, Lymphomas & Breast cancer[13]. In Anthracycline Doxorubicin (DOX), a secondary metabolites of Streptomyces Peucetiusvar. Caesius is used as very effectively[14]. However, DOX has cumulative dose effect causes cardiotoxicity. Cardiotoxicity includes Electrophysiological changes like Arrhythmia, QT prolongation, Pericarditis, Myocarditis, contractile dysfunction, decrease left ventricular ejection fraction & heart failure[12]. Cardiotoxicity is more common in hypertensive patients, diabetic, increase total cholesterol, obese & smoking persons[1-10]. Doxorubicin-induced cardiotoxicity by free radical's formation, oxidative stress on mitochondria and Cytochrome-C release apoptotic signal like caspase-8,9[2-8]. Caspase is a cysteine-aspartic proteases enzyme family have essential role in program cell death (apoptosis), inflammation & alteration of calcium ion homeostasis[35]. Doxorubicin accumulates in cardiolipin of inner mitochondrial membrane and make complex with metal ions and form ROS. ROS or free radicles activate caspase pathway leads to DNA fragmentation, lipid peroxidation which increases malondialdehyde responsible for apoptosis & necrosis. Herbal medicine safer & lesser side effect. Herbal drugs more than 50% use in world today. Herbal drugs compounds extracted from different plant species of different parts of plant-like leaves, stem, bark, root, flowers, seed, etc. Some Herbal drugs are extracted from excretory plant products such as gum, resins & latex. Herbal drugs have antioxidant & antiapoptotic potential. So, we can diminish the cardiotoxicity via cardioprotective herbal drugs (**Mangiferin, Rutin, Naringin, Crocin, Piper nigrum, Terminalia arjuna & Digitalis Purpurea**)[1-10]. The natural herbal compounds have antioxidants property by which it scavenges the free radicals and avoid excess ROS formation in the body thereby helping in mitigating cardiac diseases and several other disorders[37].

Table-1 Examples Of Antioxidants Compounds And Their Sites Of Action In Cardiac Muscles: -

Herbal compounds	Action	Site of action
Glutathione peroxidase	$2GSH+H_2O_2 \rightarrow GSSG+2H_2O$	Cytoplasm
ascorbic acid	Used as a cofactor for vitamin E	Cytoplasm
β-Carotene	Inhibits oxidation of LDL	Plasma
Vitamin-E (tocopherol)	Inhibit lipid peroxidation	Cytoplasm
ubiquinone	Redox-active electron carrier	Cell membrane
Superoxide dismutase (SOD)	$2O_2^{\cdot-}+2H^+ \rightarrow H_2O_2+O_2$	cell surface and mitochondria
Catalase	$2H_2O_2 \rightarrow 2H_2O+O_2$	Peroxisomes and mitochondria
Glutathione	Cellular reductant	Intracellular

Mechanism of action Doxorubicin induced Cardiotoxicity: -

Several multifactorial process involve in DOX-Induced Cardiotoxicity**:**

1. Oxidative Stress and Reactive Oxygen Species (ROS)
2. Mitochondrial Dysfunction
3. Apoptosis and Death Receptor Pathway
4. Inflammation
5. Calcium Homeostasis Disruption
6. Epigenetic and Genetic Factors
7. Accelerated aging and Senescence

Doxorubicin is an Anthracycline antibiotic have cumulative dose effect, it accumulates in cardiolipin inner mitochondrial membrane & makes complex with metal ions (Zn, Fe & Ca^{2+}). DOX produces reactive oxygen species (ROS)[2]. ROS enhances the intracellular calcium production & altered the calcium homeostasis which leads to oxidative stress on mitochondria. Oxidative stress on mitochondria stimulate Caspar-12, caspase-12 stimulate cytochrome-c. cytochrome-c formed apoptosome through APAF-1 & Pro-caspase-9. Apoptosome activates Caspase-3,6,7 pathways[33-38]. In another site, DOX causes Lipid peroxidation, by which TNF-α/FAS-R, MDA increase & Glutathione peroxidase decrease. MDA activate caspase-8,9 & caspase -8,9 activate, caspase-3,6,7. ROS & Caspase-3,6,7 causes DNA fragmentation & Program cell death (Apoptosis & Necrosis) which leads Cardiotoxicity & Heart Failure[13,14].

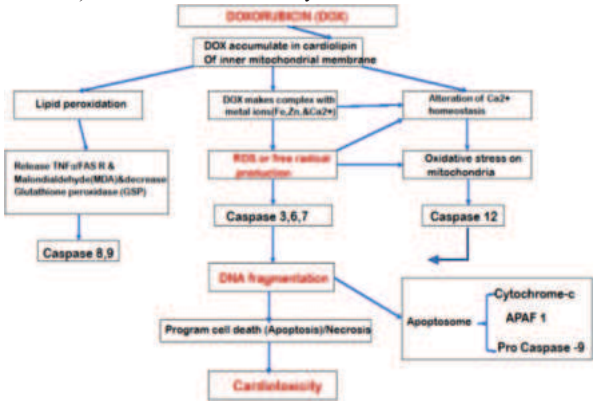


Fig. (1) Mechanism Of Action Doxorubicin-induced Cardiotoxicity

Cardioprotective Herbal Drugs: -

Herbal drugs are used to protect DOX-induced cardiotoxicity by inhibiting the free radical's formation, inhibiting the apoptotic signaling pathway & reduces the oxidative stress on mitochondria by increasing antioxidation potential. Herbal drugs have Anti-inflammatory & antioxidant property. Herbal drug also increases Superoxide dismutase(SOD), Glutathione peroxidase(GSH), Catalase(CAT) & decreases malondialdehyde(MDA), myeloperoxidase(MPO)[16-37].

Mangiferin: -

Mangiferin found in a particular species of Mango tree (*Mangifera foetida*) of family Anacardiaceae. Mangiferin is a C-glucosylxanthone which have antioxidant, iron chelating activity & anti-inflammatory action. Mangiferin also involves in intracellular calcium regulation. Mangiferin mitigates DOX-induced cardiotoxicity by iron chelation, ROS production inhibition & regulation of Ca^{2+} homeostasis[36].

Fig. (2) Mechanism Of Action Mangiferin

Withania Somnifera: -

Withania Somnifera is an herb of family Solanaceae & its common name is Ashwagandha. The main phytoconstituents of Withania Somnifera is alkaloid Withanin obtain from Root. The leaves contained steroidal lactones Withanolides. Withania Somnifera extract of Withanolides (1.5%) has antioxidant, anti-inflammatory & antitumor properties. Withanolides mitigate the Cardiotoxicity induced by Doxorubicin through production of ROS & Malondialdehyde[10].

Ginkgolide-B: -

Ginkgolides are terpene lactones obtain from *Ginkgo biloba* tree**.** They are diterpenoids with 20-carbon skeleton. Ginkgolide B(GB) is major terpenoid obtain from Ginkgolide leaves. Ginkgolide B (0.8%) & Bilobalide (3.0%) are main constituents.GB have anti-inflammatory, antioxidant, antitumor, anti-aggregating & antiaging activity. GB inhibit vasoconstriction, reduces the adhesion of platelets to endothelium & Thrombi formation. GB attenuate DOX-induced cardiotoxicity by scavenging free radicals & by anti-inflammatory action[2].

Thymol & Carvacrol: -

Thymol & Carvacrol obtain from *Thymus Vulgaris* family Lamiaceae. Thymus Vulgaris contain essential oil, and the main compound of essential oil are terpenoid Thymol & phenol isomer Carvacrol. Thymol & Carvacrol have antioxidant, antibacterial, antimicrobial & anti-inflammatory activity. The essential oil extracted by conventional steam distillation using a Clevenger apparatus. Carvacrol gives potent antioxidant activity with Vitamin-C & Vitamin-E. Thymol & Carvacrol mitigate DOX-induced cardiotoxicity by inhibiting inflammatory marker gene IL-6, TNF-α & cyclooxygenase-2[7-

Crocin: -

Crocin is a carotenoid (crocetin di–gentabios ester). It is isolated from the Saffron, dried stigma of *Crocus Sativus* & also from fruits of Gardenia farminoides Ellis. It has antioxidant, memory enhancer, sperm cryopreservation, antitumor, antiinflammation, free radical scavenging & protect against DNA damage by which Crocin cardioprotective, reduces DOX-induced cardiotoxicity[5].

Green Tea: -

Green tea obtains from leaves of Camellia sinensis by continuous fermentation. Green tea has polyphenolic antioxidant herbal compound which contained epicatechin, epigallocatechin, and epigallocatechin-3-gallate (EGCG). Green tea extract like EGCG have been studied in preclinical models in rats and mice for their capability to counter doxorubicin-induced cardiotoxicity. The following key mechanisms includes:

1. Antioxidant Activity
2. Anti-Inflammatory properties
3. Cardiac Remodeling and Functional Improvement
4. Iron Chelation

Green tea extract (GTE) decreases oxidative stress through scavenging free radicals and increases the activity of antioxidant enzyme like glutathione reductase and Glutathione-S- transferase. Specially, EGCG reduces doxorubicin-induced apoptosis through inhibiting ROS production and suppressing caspase-3 activation in cardiomyocytes. Green tea has anti-inflammatory due to catechins which inhibit the NF-kB pathway and reduces the production of inflammatory cytokines[22-34].

Grape Seed Extract: -

Grapes seed extract (GSE) is obtain from plant *Vitis vinifera*. Grape leaves have medicinal property to prevent inflammation, pain, bleeding in case of hemorrhoids.

GSE mitigates DOX-induced cardiotoxicity through the following mechanisms:

1. Antioxiant Activity
2. Anti-inflammatory

1. Iron chelation and mitochondrial protection

GSE has proanthocyanidins which scavenges free radicals and reduce lipid peroxidation and increases antioxidant enzyme activity (glutathione reductase). GSE inhibit the activation of NF-$_k$B and reduces inflammatory cytokines like (TNF-α, IL-6), improving myocardial inflammation. GSE improves hemodynamic parameters

like blood pressure, heart rate and ECG abnormalities in doxorubicin treated rates. GSE's polyphenols react with iron, interrupted the formation of doxorubicin-iron complexes that increases ROS production[4].

Glycyrrhiza: -

Glycyrrhiza glabra is also called Licorice, obtained from a herb of Leguminosae. Glycyrrhiza glabra contains bioactive compound like Glycyrrhizin, flavonoids, and triterpenoids contains bioactive compounds like glycyrrhizin, flavonoids, and triterpenoids, which have been studied for their potential to mitigate doxorubicin-induced cardiotoxicity. Glycyrrhiza has effective role in ameliorating the effect of Doxorubicin-induced cardiotoxicity by the following mechanisms:

1. Antioxidant Activity
2. Anti-Inflammatory Effects
3. Anti-Apoptotic properties

Glycyrrhiza's compounds like glycyrrhizin and flavonoids (liquiritin) have strong antioxidant effects. They counter react with reactive oxygen species (ROS) produced by doxorubicin. Glycyrrhizin reduced oxidative stress by enhancing antioxidant enzymes like superoxide dismutase (SOD) and catalase. Glycyrrhiza reduces inflammation of cardiomyocytes by inhibiting inflammatory pathways like TNF-α and IL-6. Glycyrrhiza have bioactive components like glabridin, modulate Bcl-2/Bax pathways and prohibit apoptosis and promoting cell survival[35].

Table-2 List Of Plants Which Have Cardioprotective Property: -

S. No.	Drug Name	Mechanism of action	Part used	Phytoconstituents	Reference
1	Mangiferin	Intracellular Ca^{2+} dysregulation	Fruit	C-Glucosylxanthone	36
2	Crocin	Free radical scavenging	Stigma	Carotenoids	5
3	Naringin	Free radical Scavenger & Iron chelation	Fruit	Naringin-7-o-glucoside	6
4	Withania Somnifera	Antitumor & Antioxidant	Root	Withanolide	10
5	Thymol	Inhibit TNF-α & IL-6	Leaves	Thymol & carvacrol	7
6	Grape seed	ROS inhibition	Seed	Polyphenol (proanthocyanidins)	4
7	Rutin	Antioxidant & Iron chelation	Root	Polyphenolic flavonoid	1
8	Ginkgolide-B	Free radical scavenger	Leaves	Terpenoid	2
9	Astragalus	Akt (Active kinase) & inhibit apoptosis	Root	polysaccharide	9
10	Visnazin	MDH_2 Inhibitor	Seed	Furanochromone	8

DISCUSSION: -

Doxorubicine (DOX) is an Anthracycline category of chemotherapeutic agent has very severe cardiotoxicity[35].DOX-induced cardiotoxic side effects are the principal drawback for its use. it has been many mechanisms intricate in DOX-induced cardiotoxicity but most of the plants studied are in contradiction of oxidative stress, and few have been studied for their role in apoptotic pathway and on the iron-mediated pathway. Some studies have confirmed the efficacy of herbal antioxidants as protective agents counter to oxidative stress and related diseases[50]. Treatment with Mangiferin at both 30 and 60mg/kg BW/d could reduce inflammation, hence unveiling a cardiac protective effect. Inflammation marker examination revealed that Mangiferin indeed presented protective effect against DOX-induced cardiac inflammation as specified by the significant reduction of TNF-a mRNA expression level in all groups getting Mangiferin compared to group only receiving DOX[36]. Various studies showed that the natural antioxidants had very fewer toxicity and proved to be harmless and effective. The overall antioxidants scavenge the free radicals and avoid surplus ROS development in the body thus helping in mitigating cardiac diseases and several other disorders[49]. DOX is an extensively used and successful anti-tumor drug; though, its clinical use is limited due to its Spartan cumulative dose-associated cardiotoxicity[35]. Several studies have exposed that the primary molecular mechanism intricate in DOX-induced cardiotoxicity is free radical-induced oxidative stress and cardiomyocyte death by apoptosis and necrosis[48]. By previous studies, it was remarked that the exposure of H9c2 cells to DOX significantly initiated cellular injuries, with declines in cell viability and the expression of SIRT1, as well as developments in cell apoptosis and the manifestation levels of FoxO1& P53. Resveratrol(RES) is a polyphenol that is primarily found in red wine and ensues naturally in grapes, mulberries, and peanuts. RES has abundant protective features; it can have reduced the risk of cardiovascular disease and protect cardiomyocytes from apoptosis. It has also been confirmed to protect cardiomyocytes alongside DOX-induced apoptosis. DOX-induced cardiotoxicity as specified by reduced DNA damage and histopathological alterations in the cardiac tissue of mice. Also, modern studies confirmed the bioavailability of grape seed proanthocyanidins to the target organs unveiling a greater protection beside oxidative DNA damage and oxidative stress comparative to vitamin C, E, and β carotene. In sustenance of our findings, it has been testified that various chemical compounds such as carvedilol, rosmarinic acid, dexrazoxane as well as herbal agents including grape seed extract(GSE), saffron extract and garlic extract originate to potentially be protective against DOX-induced cardiotoxicity[41]. In deduction, hemodynamic, ECG, echocardiographic, histopathologic and MTT results in this study indorse the protective effects of GSE on DOX-induced cardiotoxicity, perhaps concluded antioxidant and anti-inflammatory mechanisms. Taken together, our results sustenance the idea to present GSE as a potential drug candidate for co-administration with DOX in human chemotherapy to increase DOX therapeutic index. Additional investigations by clinical trials to inspect GSE cardioprotective effect in DOX users are essential to approve this prerogative. One more concern is the drug resistance, which is a problematic of not only DOX but all foremost cancer drugs. Three members of topmost drug efflux systems in human cancers, i.e., ABC family P-gp, MRP1, and BCRP are liable for resistance development. However, of all the plant drugs deliberated in this review, resveratrol is the only phytoconstituent reflected for its effect on mdr1 gene in DOX-induced toxicity. There are many plants and phytoconstituents evaluated for their role in averting drug resistance through P-gp mechanism. Some of them, if subjected to screening may have revealed good protective effect against DOX-induced cardiotoxicity without foremost to drug resistance. Hence, studies desired to be achieved on both acute and chronic models of toxicity with optimal doses justified through evidence[34-37].

CONCLUSION:

Herbal drugs demonstration promising another and effective treatment for chronic disorders (cardiomyopathy), against DOX-induced cardiotoxicity.Preclinical study give sufficient data on the quality certification regarding their standardization, composition, stability, and safety. Preclinical studies show the efficacy of phytochemicals like resveratrol, flavonoids, grape polyphenols, and extracts from plants such as Ixora coccinea, Datura metel, and Gymnema sylvestre in decreasing oxidative stress, enlightening antioxidant enzyme activity (e.g., SOD, CAT, GSH), and extenuating myocardial injury. These compounds frequently restore biochemical markers (e.g., CK-MB, LDH), regularize ECG parameters, and reserve cardiac structure. Herbal drugs show cardioprotective effects against doxorubicin-induced cardiotoxicity, mostly through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. It leftovers the responsibility of pharmacists, physicians, and other healthcare providers to pleat and report information on adverse effects of drugs, including herbals. Herbal drugs have presented a promising bright, and their growth using a mechanistic method can proposal well drugs for expectation of DOX-induced cardiotoxicity in future.

Conflict Of Interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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