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The Role of Nanoparticles As A Cardioprotective Strategy Against Doxorubicin Induced Cardiotoxicity

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ABSTRACT

Doxorubicin is a potent chemotherapeutic agent, but its clinical use is limited by dose-dependent cardiotoxicity, which can lead to cardiomyopathy and heart failure. This review discusses the potential of phyto constituent-based nanoformulations as cardioprotective adjuvants against doxorubicin. Encapsulating cardioprotective agents like herbal extracts, antioxidants, and anti-inflammatory co0mpounds encompassing nanoparticles enhances their bioavailability and targeted delivery to cardiomyocytes. Various nanoparticle systems including polymeric (solid lipid), inorganic (mesoporous silica, gold), and nanocomposites have shown promise in mitigating doxorubicin-induced oxidative stress, apoptosis, and cardiac injury in preclinical studies. The therapeutic effects of curcumin, resveratrol, thymoquinone, L-carnitine, and other agents were improved when delivered via nanoparticle. However, optimization of nanoparticle properties, targeted delivery strategies, long-term safety assessments, and clinical translation remain to be addressed. Nonetheless, nanoparticle-mediated delivery of cardioprotective agents holds great potential for reducing doxorubicin-associated cardiotoxicity and improving chemotherapeutic outcomes for cancer patients.

Keywords: Doxorubicin, cardiotoxicity, Nanoparticles, Cardioprotective agents, Oxidative stress, Apoptosis.

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INTRODUCTION

Cardiotoxicity, a significant and dose-limiting side effect of doxorubicin poses challenges in cancer treatment since its introduction in the 1960. This toxicity manifests as ventricular wall thinning and left ventricular chamber dilation, driven by various pathogenic mechanisms such as mitochondrial dysfunction, cardiac myocyte apoptosis, and altered calcium handling, resulting in doxorubicin-induced cardio myopathy. The following decline in the ejection fraction shows that the heart's output is hampered[1]. Recognizing herbal medicines as pivotal in alternative medicine worldwide underscores the necessity to explore their potential as primary sources for drug development and proper utilization. Eighty percent of the world's population receives basic treatment from medicinal plants, according to the World Health Organization. Chemical substances within these plants extract physiological effects on the human body, forming the basis of Indian systems of medicine, including Ayurveda, Unani, Siddha, Yoga, and Naturopathy. Given concerns about side effects associated with synthetic drugs, herbal medicines gain traction in treating conditions like hypertension, especially among a significant portion of the Indian population. Intensive studies aim to validate traditional uses of medicinal plants, ensuring their pharmacological efficacy beyond folklore. Herbal medicines offer advantages such as reduced side effects and cost-effectiveness compared to synthetic drugs. This review contributes to the development of herbal drugs with nanoparticles to increase the drug action and bioavailability then decrease fewer side effects, increased affordability, and enhanced efficacy of the drug with combination of herbal extract[2-3]. Daunomycin, epirubicin, idarubicin, and other secondary metabolites of *Streptomyces peucetius* include doxorubicin a member of the anthracycline family. These are well-established anti-neoplastic medications used to treat a range of cancers in both adults and children, such as breast cancer, lymphomas, solid tumors, and leukemia. Aside from its strong antineoplastic activity, its several toxicitiesrenal, hematological, testicular, and most significantly, cardiac toxicity, which leads to cardiomyopathy and heart failure reduce its usage in clinical chemotherapy. Doxorubicin cardiac toxic effects might happen either immediately following a single dosage or over time with repeated dose administration[4].The following is a description of doxorubicin's mechanism of action lipid peroxidation, mitochondrial damage, elevated serum total cholesterol, triglycerides, and low-density lipoprotein decreased activity of sodium (Na)+ and potassium (K+ atpase), release of vasoactive amines, ions pairing in myocardial adrenergic signaling & regulation and myocardial injury from free radicals .Doxorubicin inhibits cell activity and induces cytolysis by releasing reactive oxygen species such hydrogen peroxide and superoxide anion. The mechanism by which doxorubicin causes damage to the myocardium

revolves around the release of free radicals. Additionally, it raises serum enzyme levels including CPK6 and LDH[5]. The physical characteristic of Doxorubicin is a red, crystalline substance with no smell. It is insoluble in non-polar organic solvents, soluble in anhydrous methanol, and soluble in water and aqueous alcohols. It is stable in a closed container at room temperature under typical storage circumstances[6]. Chest pain or dyspnea with effort. All-over weakness and exhaustion Ventricular fibrillation, palpitations can result from abnormal heartbeats. Heart failure, the feet, ankles, and legs swell, Elevated blood pressure, Excessive cholesterol these are effects on the body[7].

Doxorubicin (Mechanism in cancer, Adverse effect cardiotoxic)

Doxorubicin is an anthracycline antibiotic widely used as a chemotherapeutic agent in the treatment of various cancers, including breast cancer, ovarian cancer, bladder cancer, and lymphomas. Its mechanism of action in figure1 cancer cells is multifaceted, but it primarily works by intercalating with DNA, inhibiting topoisomerase II, and generating free radicals that damage cellular components, ultimately leading to cell death.

Mechanism of Action in Cancer:

DNA intercalation: Doxorubicin can intercalate between the base pairs of DNA disrupting the normal structure and function of the DNA molecule, which interferes with DNA replication and transcription processes.

Topoisomerase II inhibition: Doxorubicin inhibits the activity of topoisomerase II, an enzyme responsible for untangling DNA strands during replication and transcription. This leads to the accumulation of DNA double-strand breaks, which can trigger apoptosis (programmed cell death) in rapidly dividing cancer cells.

Free radical generation: Doxorubicin can undergo redox cycling, generating reactive oxygen species (ROS) such as superoxide and hydroxyl radicals. These free radicals can cause oxidative damage to cellular components, including DNA, proteins, and lipids, ultimately contributing to cell death.

Induction of apoptosis: Through its various mechanisms of action, doxorubicin can trigger apoptosis, a programmed cell death pathway, in cancer cells, thereby reducing tumor growth and progression.

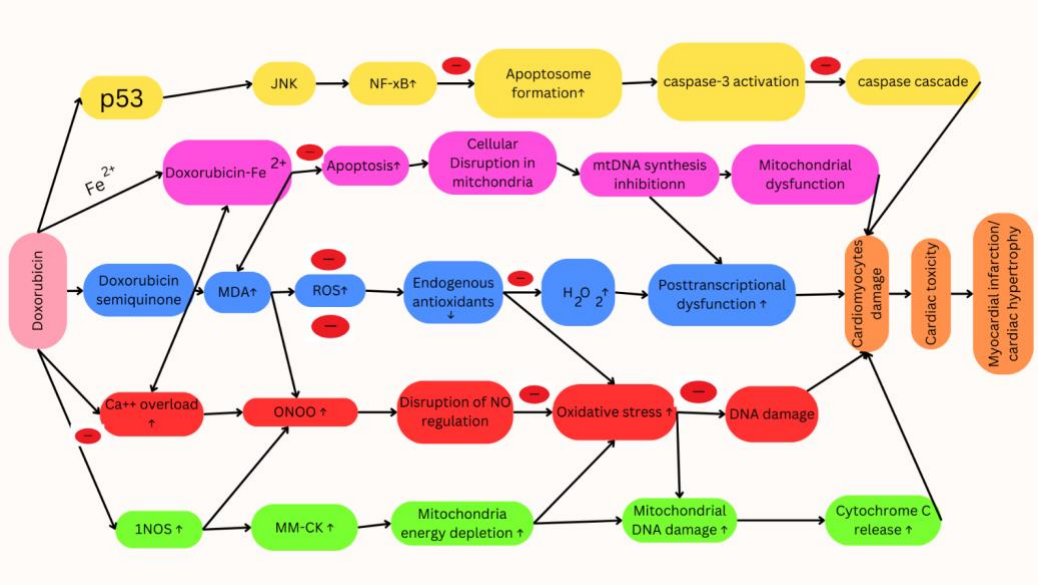

Figure 1: Mechanism of doxorubicin inducing cardiotoxicity

The figure 1 show to be a flowchart or a pathway diagram illustrating various cellular processes and their interconnections, particularly focusing on stress response, apoptosis (programmed cell death), and mitochondrial dysfunction. The diagram uses different colors to categorize processes

- Yellow: Apoptotic pathway.
- Pink: Cellular disruption and mitochondrial dysfunction.
- Blue: Antioxidant and transcriptional processes.
- Red: DNA damage and stress response.
- Green: Mitochondrial energy processes.

The pathways start with key players like p53 (a tumor suppressor) and lead through various intermediates (like JNK, NF-κb, ROS) to outcomes such as caspase activation (leading to apoptosis), mitochondrial dysfunction, and DNA damage. The diagram suggests that these processes are interconnected and can influence each other, showing the complexity of cellular stress responses and the balance between survival and death pathways. Then also mechanism of doxorubicin inducing cardiotoxicity illustrates the various pathways and processes involved in how the chemotherapy drug doxorubicin can cause adverse effects on the heart.

Doxorubicin (in pink color) triggers several processes

A. Apoptosis (programmed cell death)

B. Cellular disruption of mitochondria

C. Mrna synthesis inhibition

D. Mitochondrial dysfunction

Another pathway starts with p53 (a tumor suppressor protein), leading to JNK and NF-κb, eventually causing apoptosome formation, caspase-3 activation, and caspase cascade. A parallel pathway (in blue) involves downregulation of semiquinone, NADH, and ROS (reactive oxygen species), leading to endogenous antioxidants, H_2O_2, and post-transcriptional dysfunction. A red pathway shows AKT/mtor inhibition, $ONOO^-$ formation, disruption of NO regulation, oxidative stress, and DNA damage. A green pathway depicts inos↑, mnsod↑, mitochondrial energy depletion, mitochondrial DNA damage, and cytochrome C release. The various pathways converge on outcomes such as myocardial structural damage, contractile dysfunction, and myocardial dysfunction by apoptosis. The figure 1 shows that doxorubicin-induced cardiotoxicity involves multiple interrelated pathways, including apoptosis, mitochondrial dysfunction, oxidative stress, DNA damage, and disruption of cellular processes, ultimately leading to heart muscle damage and dysfunction.

Adverse Effect: Cardiotoxicity

Despite its effectiveness as an anticancer agent, one of the major adverse effects associated with doxorubicin is cardiotoxicity, which can lead to potentially life-threatening complications such as congestive heart failure, arrhythmias, and cardiomyopathy. The cardiotoxicity of doxorubicin is believed to be primarily mediated by oxidative stress and free radical generation, which can damage cardiomyocytes (heart muscle cells) and impair cardiac function. The proposed mechanisms of doxorubicin-induced cardiotoxicity include:

Free radical formation: Doxorubicin can generate free radicals through redox cycling, leading to oxidative stress and damage to cardiac cells.

Mitochondrial dysfunction: Doxorubicin can disrupt mitochondrial function in cardiomyocytes, leading to impaired energy production and increased oxidative stress.

Myocardial cell death: Prolonged exposure to doxorubicin can induce apoptosis and necrosis of cardiomyocytes, leading to myocardial damage and impaired cardiac function.

Disruption of calcium homeostasis: Doxorubicin can interfere with calcium handling in cardiomyocytes, leading to contractile dysfunction and arrhythmias.

Impaired cellular repair mechanisms: Doxorubicin may inhibit the ability of cardiac cells to repair and regenerate, exacerbating the cumulative damage over time[8-11].

Nanoparticle

In general, nanoparticles are defined as tiny particles with sizes ranging from 1 nm to 100 nm. The most researched nanomaterial is silver nanoparticles[12]. Silver nanoparticles vast surface area makes it possible for them to come into more contact with microbes, which influences their potent

antimicrobial action. Because these metabolites are bioactive substances that may operate as capping and reducing agents, no additional chemical agent is required to produce the nanoparticles[13-16].

Origin of Nanomedicine

Nanomedicine is an emerging field that combines knowledge from various disciplines, including nanotechnology, medicine, biology, and engineering. The concept of nanomedicine originated from the idea of manipulating materials at the nanoscale (1 to 100 nanometers) for medical applications. Here's a brief overview of the origin of nanomedicine from a research article. According to the article "Nanomedicine: Evolution of an emerging strategy for disease treatment and diagnosis" by Subramani et al. (2010), the term "nanomedicine" was first introduced in the early 1990s by Robert A. Freitas Jr., a pioneer in the field of nanotechnology. Freitas envisioned the use of nanorobots for medical applications, such as targeted drug delivery and cellular repair. The article further states that the concept of nanomedicine gained significant attention after the development of various nanoparticles and nanostructures in the late 1990s and early 2000s. Researchers began exploring the potential of these nanomaterials for drug delivery, imaging, and diagnostics. One of the key developments that contributed to the growth of nanomedicine was the synthesis of nanoparticles with specific properties, such as size, shape, and surface chemistry, which allowed for targeted drug delivery and improved bioavailability. Additionally, the ability to functionalize nanoparticles with biomolecules, such as antibodies or peptides, enabled the development of targeted therapies for various diseases[17].

Nanoparticles in doxorubicin induced cardiotoxicity (DIC)

Thymoquinone (TQ) and its nanoparticle formulation (TQ-nps) show potential in alleviating doxorubicin-induced cardiotoxicity. The combination of TQ or TQ-nps with doxorubicin (DOX) significantly reduced DOX-induced cardiotoxicity in mice implanted with colon (HCT116) and breast (MDA-MB-231-Luc) cancer cell lines. Histo pathological analysis of heart sections showed that TQ + DOX and TQ-nps + DOX groups showed a significant reduction in cardiac damage induced by DOX compared to the DOX alone group. The authors suggest that the nano formulation of TQ (TQ-nps) protects cardiomyocytes against DOX-induced cardiotoxicity, like free Deadlier studies referenced in the article also support the protective role of TQ against DOX cardiotoxicity by modulating oxidative damage and cellular inflammation. The nanoparticle formulation of TQ appears to offer similar cardioprotective benefits as free TQ when combined with doxorubicin chemotherapy. The nanoparticles may improve the bioavailability and targeted delivery of TQ, thereby enhancing its ability to alleviate the cardiotoxic effects of doxorubicin.

Overall, the authors propose TQ and its nano formulation as promising adjuncts to doxorubicin therapy to reduce cardiotoxicity while keeping anticancer efficacy[18].PLGA nanoparticles were loaded with doxorubicin up to 5% drug weight/weight. The nanoparticles had an average diameter of around 130 nm. They were surface-modified by conjugating poly (ethylene glycol) (PEG) to the nanoparticle surface using an avidin-biotin coupling system. Pegylation increased the circulation time of the doxorubicin-loaded non-pegylated nanoparticles. In mice studies, the pegylated doxorubicin loaded PLGA nanoparticles showed reduced cardiotoxicity compared to free doxorubicin, as measured by decreased changes in serum creatine phosphokinase levels, left ventricular function, and histopathology, while supporting anti-tumor efficacy against lymphoma cells. So, in summary, the nanoparticle formulation was pegylated PLGA nanoparticles which encapsulated doxorubicin and reduced its cardiotoxic effects compared to free doxorubicin when tested in mice[19].

Role of chemical compound and Nanoparticle against Doxorubicin induced Cardiomyopathy:

The illness cardiomyopathy is treated with a variety of chemical compound and nanoparticles. When treating cancer patients with doxorubicin, cardiotoxicity is a significant dose-limiting issue. The specific toxicity of doxorubicin to cardiac cells results from drug accumulation that generates free radicals within the cardiac cells. The nuclear envelope, mitochondria (NADH dehydrogenase), cytosol (xanthine oxidase), and sarcoplasmic reticulum (NADPH cytochrome P-450 reductase) are the sites of free radical production in cardiac cells because of the one-electron reduction of doxorubicin. Heart mitochondrial semiquinones appear to react more preferentially with hydrogen peroxide than do doxorubicin-generated semiquinone radicals in liver microsomes, which preferentially react with molecular oxygen to form safe superoxide radicals. This reaction results in the highly reactive hydroxyl radical. Compared to liver microsomes, cardiac tissue sarcosomes have higher levels of NADPH cytochrome P-450 reductase positivity Incapable of reducing doxorubicin to its semiquinone due to a relatively low. The quine ring, which is a part of the tetracycline molecule, alternates between quinone and semiquinone. This process results in the production of free radical species, damage to cardiomyocytes, and cardiomyopathy when generated electrons are absorbed by oxidizing substances like oxygen[20].

Table 1: Nanoparticles Used Against Doxorubicin Induced Cardiomyopathy

S. No	Synthetic/ Herbal Compound Loaded Nanoparticles	Pharmacological Activities	In-vitro/In-vivo	Dose & Duration	Size of Formulation & Zeta Potential	Molecular Aspects	Re.
1	Curcumin loaded gold nanoparticle (Cur-Au nps)	Anti-inflammatory, Anti-Microbial, Antioxidant and Cardioprotective	In- Vivo [Mice]	0.4 mg/kg & 14 days	32.0nm & -	↑ Bcl-2 and ↓ Bax, Caspase	21
2	Fullerenol nanoparticle (Fe^{2+} nps)	Anti-Inflammatory, Anticancer	In-Vivo [Male Wistar Rats]	0.06mg/kg & 1 day	20 nm & -30.8 mv	↓ Catalase, mnsod and Oxidative Stress in mrna level	22
3	Idebenone nanoparticle (IDB nps)	Antioxidant, Cardioprotective	In-Vivo [Male Wistar rats]	50mg/kg & 18 days	1 µm &-	↓ CK-MB AND LDH	23
4	Resveratrol loaded solid lipid nanoparticle (Res- SL nps)	Anti-Inflammatory, Antitumor, Antioxidant and Cardioprotective	In- Vivo [SD rats]	1000mg/kg & 7 days	271.1nm & -25.8 ± 0.33 mv	Vacuoles degeneration of different sizes, Myocardial fibers were arranged regularly	24
5	Moringa Oleifera extract loaded L-carnitine nanoparticle (L-C nps)	Antioxidant, Anti-Inflammatory and Anti-Apoptotic	In-Vivo [Male Albino rats]	50mg/kg & 28 days	-	↓CK, LDH, ALT, CRP, ↓MDA, NO, HO-1 and NF-Kβ	25
6	Apigenin loaded gold nanoparticle (Api-Au nps)	Anti-Apoptotic and Cardioprotective	In-Vivo [Male Wistar rats] & In-Vitro [H9c2 cell line]	25mg/kg & 12 days	21.4 ± 11.6 nm & -	↓ Bax, Caspase-3 and ↑ Bcl-2	26
7	Curcumin loaded Mesoporous Silica nanoparticle (msnps)	Anti-Inflammatory, Antioxidant and Cardioprotective	In-Vivo [Albino rats]	200mg/kg & 14 days	216.9 ± 7.6 nm	↑CK-MB, LDH, GSH, SOD, CAT and↓ Lipid peroxidation	27
8	*Tamarindus indica* pulp loaded Magnesium oxide nanoparticle (mgonps)	Antioxidant, Cardioprotective and Lipid-lowering agent	In-Vitro [BHK-21] In-Vivo[Wistar albino rats]	30mg/kg & 28 days	-	↓ Caspase-3, p53 and ↑ Bcl-2 and SOD	28
9	Ginger extract loaded Chitosan nanoparticle (GE-C nps)	Antioxidant, Anti-Inflammatory, Antidiabetic and Anticancer	In-Vitro[hepg2 cell line] In-Vivo[Swiss albino mice]	1mg/ml & 12 weeks	72.8 ± 20.6 nm & +15.66±0.78 mv	↓MDA, CK, LDH, Bcl-2, CK-MB and TNF-α	29
10	Berberine micellar nanoformulation	-	In-Vivo [Wistar rats]	& 28 days	-	↓LDH, CK-MB, ctn-1, MDA ↑SOD and CAT	30

Curcumin Loaded Gold Nanoparticle

DOX is a widely used chemotherapy drug, but its use is limited by its cardiotoxic effects. Sharifighdam et al. Synthesized Cur-aunps and demonstrated its efficacy against DOX-induced cardiotoxicity. In this, curcumin used as both reducing and capping agent for synthesizing gold nanoparticles. Characterization showed that Cur-aunps had an average size of 9.6 nm. In a mouse model of DOX-induced acute cardiotoxicity, treatment with Cur-aunps (400µg/kg) prevented increases in serum cardiac injury markers like LDH, CK-MB, troponin I, in addition, Nano formulation demonstrated to mitigate morphological (body and heart weight loss), myocardial histological changes, and cardiomyocyte apoptosis by downregulating Bax, Caspase-3 and upregulating Bcl-2 in comparison to free curcumin[31-37]. These results suggest that Curcumin-coated gold nanoparticles showed promising protective effects against DOX-induced acute cardiotoxicity in mice, suggesting their potential in alleviating side effect associated with DOX during chemotherapy[21].

Fullerenol Nanoparticle

Seke et al. Synthesized and studied the nanocomposite made of fullerenol nanoparticles (FNP) and iron ions (Fe2+), denoted as FNP/Fe2+. Owing to its antioxidant qualities and its ability to scavenge the free radicals, Fullerenol C60(OH)24 may offer some protection against oxidative stress induced by Doxorubicin. The FNP/Fe2+ nanocomposite was characterized by DLS and TEM-EDS. The results suggested that the Fe^{2+} ions successfully bound to the Fullerenol nanoparticle, and the Particle size ranges from 11 to 60 nm. When compared to doxorubicin alone, pretreatment with FNP/Fe^{2+} nanocomposite one hour before to doxorubicin injection dramatically decreased the adverse effects on the liver and heart tissues in a rat model. At the ultrastructural level, FNP/Fe2+ pretreatment mitigated the morphology of cardiomyocytes and hepatocytes, with only sporadic alterations. The Gene expression analysis showed the downregulation of antioxidant enzymes catalase and mnsod in the FNP/Fe2+ + doxorubicin group, showing reduced oxidative stress compared to doxorubicin alone. Seke et al. Propose that the protective effects are due to the antioxidant capability of fullerenol and its ability to chelate excessive iron released by doxorubicin, avert the iron-mediated oxidative damage. The FNP/Fe2+ nanocomposite showed the potential effect in mitigating doxorubicin-induced cardiotoxicity and hepatotoxicity in rats, suggesting its application as a protective nanocarrier system for chemotherapeutic drugs[22].

Idebenone Nanoparticles

The evalution of the nanoparticle with the intention of increasing the idebenone's aqueous solubility and, its pharmacological performance. Ghule et al. Demonstrated the study of the IDB's

nanosizing particles greatly enhanced the water solubility, which in turn enhanced the release profile of IDB nanoparticles. The outcomes also showed that doxorubicin was the cause of the development of Reactive Oxygen Species (ROS), which caused the cardiomyopathy in rats. On the other hand, the generated IDB nanoparticles had a positive impact on cardiac state in the cardiomyopathy which is caused by the dapsone. The Idebenone nanoparticle's antioxidant characteristics contributes to cardio protection in doxorubicin-induced cardiomyopathy. Treatment with the Idebenone nanoparticle drive into the increase in ventricular contractile dysfunction and hypertensive cardiac injury caused by doxorubicin. The findings of the study suggested that idebenone, when transformed into nanoparticulate form, may function as a possible cardioprotective formulation in cardiomyopathy caused by doxorubicin[23].

RES- Loaded Solid Nanoparticles

Doxorubicin (DOX) is a potent chemotherapy drug, but its clinical use is limited by dose-dependent cardiotoxicity. Resveratrol (Res) is a natural polyphenol that can ameliorate cardiomyocyte calcium cycling and inhibit DOX-induced cardiotoxicity but has poor water solubility. Zhang et al. Developed the Res-loaded solid lipid nanoparticles (Res-SLN) using an emulsification-diffusion method followed by sonication. The optimized Res-SL nanoparticle had a particle size of 271 nm. It showed the sustained release of the resveratrol over 30 hours and thus improved the oral bioavailability of resveratrol in rats compared to a Res-lipid physical mixture. In a mouse model of DOX-induced cardiotoxicity, Res-SLN treatment improved heart rate, ejection fraction, fractional shortening and myocardial histopathology compared to free resveratrol[38]. The results also suggest that encapsulating resveratrol in a solid lipid nanoparticle formulation enhances its therapeutic efficacy against DOX-induced cardiotoxicity, likely improving the resveratrol's solubility, bioavailability and delivers it to cardiomyocytes. This nanoparticle formulation of resveratrol shows promising cardioprotective adjuvant therapy during doxorubicin chemotherapy by mitigating the DOX-induced cardiac dysfunction and injury[24].

L-carnitine nanoparticles (LCNPS)

DOX is a potent chemotherapeutic drug and causes Cardio toxicity on its continuous use. Motelp et al. Explored the Synergistic effects of L-car nitine nanoparticles (lcnps) and Moringa oleifera extract against DOX-induced cardiac toxicity in male rats. DOX treatment augmented the levels of oxidative stress markers such as MDA, NO, HO-1 and inflammatory marker NF-κb[44], cardiac injury markers like CK, LDH, ALT, troponin-1, endothelin-1 and caused some histological alterations in cardiac tissue[45-46]. Treatment with L-cnps or Moringa oleifera extract alone could partially alleviate the changes by downregulating the oxidative stress, inflammation and cardiac

injury markers. However, the co-administration of L-cnps and Moringa oleifera extract exhibited the synergistic effect in reversing all the biochemical parameters and histological changes near the normal levels. The cardioprotective effects were attributed to the antioxidant, anti-inflammatory and radical scavenging properties of L-cnps and bioactive compounds present in Moringa oleifera. Thus, the study concluded that combination treatment could be a promising approach for mitigating DOX-induced cardiotoxicity by suppressing oxidative stress and boosting antioxidant status. Nano formulation of L-carnitine showed the enhanced therapeutic efficacy against DOX-induced cardiomyopathy when combined with the antioxidant-rich Moringa oleifera extract in the rat model study[25].

Gold Nanoparticles

Sharifiaghdam et al. Synthesized the Api-aunps using apigenin (Api). It was used as a reducing and capping agent. The result of the characterization of Api-aunps showed that the average size of nanoparticle was found to be 21.4 ± 11.6 nm. In an in- vitro study on the H9C2 cell line, Api-Au nps manifest that no toxicity up to 50 ppm concentration. In a rat model of doxorubicin-induced cardiotoxicity, treatment with Api-Au nps hindered the body weight and the heart weight loss compared to doxorubicin alone. Api-aunps downregulated the serum levels of cardiac injury markers like LDH, CK-MB, and ctn-I compared to doxorubicin alone. Histological analysis exhibited that Api-aunps guaranteed against doxorubicin-induced myocardial damage[39-41]. Api-aunps inhibited cardiomyocyte apoptosis by upregulating the Bcl-2 and reducing Bax and caspase-3 expression compared to doxorubicin alone[26].

Mesoporus Silica Nanoparticles

Curcumin, a natural compound from turmeric, has shown cardioprotective effects, but its clinical use is limited due to poor aqueous solubility and bioavailability. Yadav et al. Synthesized Mesoporous silica nanoparticles (msns) which is used to load the curcumin for improving its solubility, dissolution, and bioavailability. Curcumin-loaded msns (Cur-msns) were fabricated by the wetness impregnation method. The synthesized nanoparticles were characterized by SEM, particle size analysis, drug content, and entrapment efficiency. In –Vivo study was demonstrated on rats, DOX induced cardiomyopathy associated with increased levels of cardiac biomarkers like CPK, LDH[42] and oxidative stress by upregulating MDA, downregulating GSH, SOD, CAT, and histopathological changes. Prior treatment with curcumin alone and Cur-msns significantly shielded the myocardium from DOX-induced toxic effects by bringing down the oxidative stress and restoring antioxidant levels. Cur-msns showed superior cardioprotective effects compared to free curcumin, attributable to the improved bioavailability of curcumin delivered via the MSN

system and it was shown by higher C max and AUC values in the pharmacokinetic study[43]. The results suggest that delivering curcumin through mesoporous silica nanoparticles can be an effective strategy to enhance its bioavailability and cardioprotective effects against doxorubicin-induced cardiomyopathy. The study shows the potential of using mesoporous silica nanoparticles as a delivery system to improve the bioavailability and therapeutic efficacy of curcumin in protecting against doxorubicin-induced cardiotoxicity[27].

***Tamarindus Indica* Pulp Loaded Magnesium Oxide Nanoparticles**

Tamarind pulp-derived magnesium oxide nanoparticles (Pulp mgo nps) against doxorubicin-induced cardiomyopathy Pulp mgo nps were successfully synthesized using a green approach with tamarind pulp extract. They were characterized by various techniques like UV-vis, XRD, FTIR, SEM-EDX. In vitro antioxidant assays (DPPH, ABTS, iron chelating, nitric oxide scavenging) showed significant antioxidant activity of Pulp mgo nps. They also inhibited hemolysis and lipid peroxidation ex vivo. Pulp mgo nps were non-toxic to BHK-21 and Vero cell lines at tested doses up to 1000 mg/Ml. In a rat model of doxorubicin-induced cardiomyopathy Pulp mgo nps at 15 and 30 mg/kg body weight doses ameliorated the increase in cardiac injury biomarkers (troponin I, CK-MB, AST) caused by doxorubicin. They normalized the dysregulated lipid profile (cholesterol, triglycerides, LDL, HDL). They restored the altered antioxidant levels (SOD, catalase, GSH) and reduced lipid peroxidation in cardiac tissue. They downregulated apoptotic genes (caspase-3, p53) and upregulated the anti-apoptotic Bcl-2 gene. They upregulated antioxidant genes (SOD, catalase, gpx). Histological analysis showed they preserved cardiac morphology. The 30 mg/kg dose of Pulp mgo nps exhibited better cardioprotective effects compared to 15 mg/kg dose. The biogenic tamarind pulp-derived mgo nanoparticles demonstrated promising cardioprotective potential against doxorubicin-induced cardiomyopathy through their antioxidant, hypolipidemic and anti-apoptotic activities in the rat model[28].

Ginger Extract Loaded Chitosan Nanoparticles

Ginger extract (GE) and the chemotherapeutic drug doxorubicin (DXN) were loaded into chitosan nanoparticles (cnps) to investigate their effects against hepatocellular carcinoma (HCC) in mice. Loading DXN into cnps decreased cardiac levels of malondialdehyde (MDA, a marker of oxidative stress) and tumor necrosis factor-α (TNF-α, a pro-inflammatory mediator) compared to free DXN treatment. GE alone and especially the GE-loaded cnps reduced cardiac MDA and TNF-α levels compared to control and DXN groups. The combination of DXN-loaded cnps and GE-loaded cnps showed the greatest reduction in cardiac MDA and TNF-α levels compared to all other treatment groups. Serum activities of lactate dehydrogenase (LDH) and creatine kinase-MB (CK-

MB), which are markers of cardiac injury, were significantly lower in mice treated with the combination of DXN-cnps and GE-cnps compared to other groups. Encapsulating DXN and GE in the cnps helped reduce doxorubicin's cardiotoxic effects, with the combination nanoparticle formulation providing the most pronounced cardioprotective effects in HCC-bearing mice, likely through reducing oxidative stress, inflammation and cardiac enzyme leakage[29].

Berberine Micellar Nano Formulation

The researchers developed berberine-loaded polymeric nano micelles (mber) using Pluronic F127 and evaluated their efficacy in mitigating doxorubicin-induced cardiotoxicity in the H9c2 embryonic cardiomyocyte cell line. Doxorubicin treatment caused significant cardiotoxicity in H9c2 cells, as evidenced by reduced cell viability, increased leakage of lactate dehydrogenase (LDH), creatine kinase myocardial band (CK-MB), and cardiac troponin I (ctn-I), elevated oxidative stress, inflammation, and apoptosis. Treatment with free berberine (Ber) partially protected against doxorubicin-induced cardiotoxicity. The berberine-loaded nanomicelles (mber) showed significantly higher cardioprotective efficacy compared to free berberine when co-administered with doxorubicin. Mber co-treatment with doxorubicin resulted in improved cell viability, reduced leakage of cardiac injury markers, attenuated oxidative stress (reduced MDA, restored GSH, catalase and SOD levels), suppressed inflammation (reduced IL-1β and IL-6 levels), and inhibited apoptosis (reduced caspase 3/7 activity) compared to doxorubicin alone or doxorubicin + free berberine groups. The Nano formulation of berberine in polymeric micelles (mber) enhanced its cardioprotective effects against doxorubicin-induced toxicity in cardiomyocytes compared to free berberine, suggesting mber as a promising approach to mitigate doxorubicin-associated cardiotoxicity[30].

Highlights of Study

Targeted delivery strategies: Developing nanoparticles with specific targeting moieties, such as antibodies or peptides, could improve their accumulation in the myocardium and minimize off-target effects in other organs.

Combination therapy approaches: Exploring the synergistic effects of nanoparticles loaded with different cardioprotective agents, or combining nanoparticle therapy with other cardioprotective strategies, could lead to the improved therapeutic outcomes.

Mechanistic studies: While the review highlights the potential mechanisms of cardio protection by various nanoparticle formulations, further in-depth mechanistic studies are needed to elucidate the precise molecular pathways involved and find potential targets for intervention.

CONCLUSION AND FUTURE PERSPECTIVE:

In recent days, phyto constituents loaded nanoparticles are used for the targeted drug delivery systems and for the increased activity. The nanoparticle formulations mentioned in this study such as curcumin-loaded gold and mesoporous silica nanoparticles, fullerenol nanoparticles, idebenone nanoparticles, resveratrol-loaded solid lipid nanoparticles, L-carnitine nanoparticles, and apigenin-loaded gold nanoparticles showed promising cardioprotective effects in mitigating doxorubicin-induced cardiotoxicity. Optimization of nanoparticle properties size, shape, surface charge, and other physicochemical properties of nanoparticles can significantly affect their pharmacokinetics, biodistribution, and efficacy. In-depth mechanistic studies of the nanoparticles are needed for us to elucidate the precise molecular pathways that are involved in treating the doxorubicin-induced cardiotoxicity and for finding the potential targets of the nanoparticles for intervention. Doxorubicin can inhibit topoisomerase II and interfere with DNA replication and transcription; it does not delve into how doxorubicin might alter the expression of specific cardiac genes or induce epigenetic changes (such as DNA methylation or histone modifications) that could contribute to long-term cardiotoxicity. This aspect is important because changes in gene expression and epigenetic modifications can have lasting effects on cardiac function and contribute to the development of cardiomyopathy, even after the cessation of doxorubicin treatment. It's worth noting that the focus of this review is primarily on nanoparticle-based strategies to mitigate doxorubicin-induced cardiotoxicity, so it may not cover all the known pathways of doxorubicin cardiotoxicity in depth. The authors have concentrated on pathways that are most relevant to the protective mechanisms of the nano formulations they discuss, such as antioxidant and anti-apoptotic effects. Based on the above-mentioned aspects the researchers can further advance the field of nanoparticle-based cardioprotective strategies against doxorubicin chemotherapy and to potentially expand its therapeutic applications. Future studies should focus on perfecting these properties to enhance the targeted delivery and cardioprotective effects of the nanoparticles. Long-term safety and toxicity assessments of nanoparticles warranted to enhance release over extended period and accumulation in various tissues before their clinical translation. The results were shown to be promising in preclinical studies with the use of nano formulation, and thus this area of research can be further translated into human trials with the utilization of the development of scalable manufacturing processes to evaluate the efficacy and safety of nanoparticle-based cardioprotective therapies. In addition to the nanoparticle formulations discussed in the review, future research should be carried out by delve into alternative nanocarriers such as liposomes, micelles, or polymeric nanoparticles, dentrimers, quantum dots and rods etc., for delivering natural

based nano formulation as cardioprotective agents against doxorubicin-induced cardiotoxicity. By addressing these aspects, researchers can further advance the field of nanoparticle-based cardioprotective strategies, ultimately improving the safety and efficacy of doxorubicin chemotherapy and potentially expanding its therapeutic applications.

CONCLUSION

This review highlights the promising potential of nanoparticle-based formulations as cardioprotective adjuvants during doxorubicin chemotherapy. By encapsulating cardioprotective agents like herbal extracts, antioxidants, and anti-inflammatory compounds into nanoparticles, researchers have demonstrated enhanced bioavailability, targeted delivery to cardiomyocytes, and improved therapeutic efficacy against doxorubicin-induced cardiotoxicity. Various nanoparticle systems including polymeric (solid lipid), inorganic (mesoporous silica, gold), and nanocomposites have shown remarkable ability to alleviate oxidative stress, reduce cardiomyocyte apoptosis, preserve cardiac function, and mitigate biochemical and histological markers of cardiotoxicity, evidenced through preclinical studies. While encouraging, challenges like optimization of nanoparticle properties, targeted delivery strategies, long-term safety assessments, and clinical translation need to be addressed before these nanoparticle formulations can be implemented clinically. Nonetheless, integrating nanotechnology with cardioprotective agents represents a promising avenue to mitigate doxorubicin-induced cardiotoxicity and improve treatment outcomes for cancer patients undergoing chemotherapy.

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