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SYSTEMATIC REVIEW ON CARDIO-PROTECTIVE EFFECT OF HERBS/NATURAL COMPOUNDS IN DOXORUBICIN TOXICITY

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ABSTRACT

This study aimed to assess the possible effect of various natural compounds against cardiotoxicity caused by doxorubicin. In accordance with the PRISMA guidelines, an extensive and recent search was performed across various electronic databases, such as Web of Science, Scopus and PubMed. A total of 25 out of 27 studies were screened according to the predetermined inclusion and exclusion criteria, leading to the identification of 06 eligible articles for this systematic review. The study observed that doxorubicin treatment decreases cell viability and enhances mortality. Co-administration of natural compounds showed protective effects, reversing these harmful outcomes caused by doxorubicin. Furthermore, doxorubicin also dramatically changed biochemical parameters and caused histological alterations in cardiac tissue, but co-treatment almost completely reverted these changes, bringing them nearer to control values. The results indicated that natural herbs protect against doxorubicin-induced cardiotoxicity by their antioxidant and anti-inflammatory effects.

Keywords: ***Ayurveda,*** *Cardiotoxicity, Doxorubicin, PRISMA*

INTRODUCTION

Doxorubicin is an anthracycline antibiotic drug, widely used in cancer chemotherapy. Doxorubicin is used extensively for the treatment of many types of cancers, such as lymphomas, lung cancer, acute leukemia, testicular cancer, ovarian cancer, breast cancer and thyroid cancer [1]. Although highly effective, one of the principal limitations of doxorubicin is its multidrug toxicity to several organs, most notably the heart. This cardiotoxicity can be manifested as congestive heart failure, ventricular dysfunction and arrhythmias. The clinical application of doxorubicin is considerably hampered by its cardiotoxicity, stimulated mainly by oxidative stress and mitochondrial injury to cardiac cells [2-4]. These unfavorable effects can be prevented using combination therapy. The co-administration of doxorubicin with other substances that have chemo-protective activity has resulted in decreased normal tissue toxicity. In this regard, greater emphasis has been placed on natural products and herbal extracts because of their putative anti-inflammatory, cardioprotective and antioxidant activities [5, 6]. The present research paper intends to tackle this issue and demonstrate a systemic study to understand the cardioprotective effect of some herbs and natural compounds in doxorubicin-induced cardiotoxicity.

AIM & OBJECTIVE:

This systematic review consolidated existing research to provide comprehensive information on **the** cardioprotective effect of herbs in doxorubicin toxicity.

Methods

An extensive literature search was conducted using various databases, including PubMed, Web of Science, Google Scholar, and Scopus. Recent and reputed publications that explored the cardioprotective action of medicinal herbs against doxorubicin-induced cardiotoxicity were included. The keywords used in searching included "Doxorubicin cardiotoxicity," "herbal cardio-protection," "natural antioxidants," and "co-administration of herb". Study selection and data extraction were as per PRISMA guidelines.

Inclusion Criteria:

- Full text and peer-reviewed scientific articles in the English language
- Specific studies examined the role of herbs/natural compounds in doxorubicin-induced cardiotoxicity
- Sufficient and conclusive findings of studies
- Studies published in recent years

Exclusion Criteria:

- Non-relevant articles
- Review articles, case reports and book chapters
- Letters to editors and oral presentations, etc.

Data Extraction Process

Two researchers double-checked every potential study and extracted the data, which included the name of the author and year of publication, model of study, doxorubicin dose, administration regimen, and effect on cardiac tissue or cells. Information on the administration protocol and effects of co-administered herbs was also noted. The articles were chosen according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart, as mentioned in **Figure 1**.

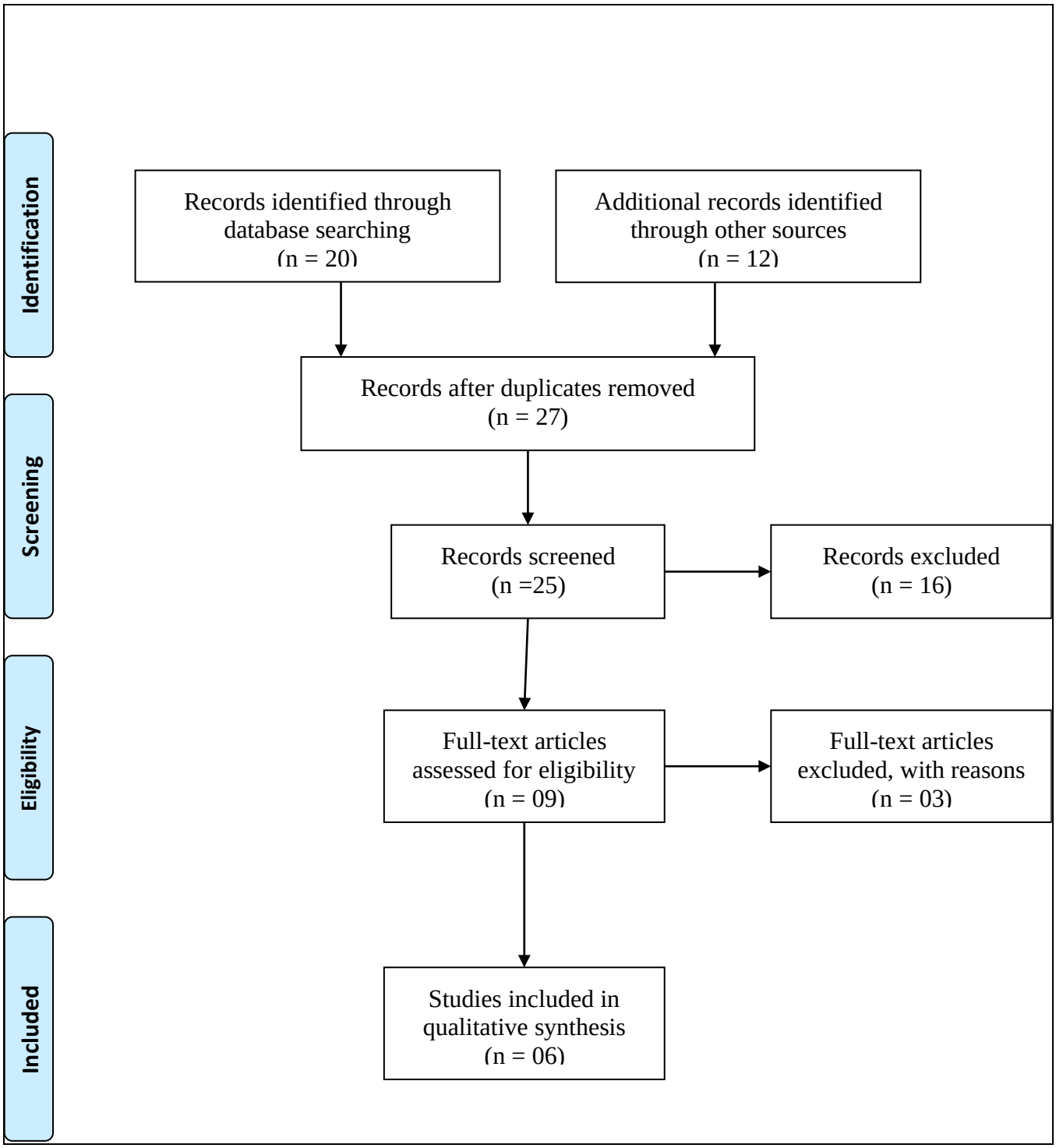

Figure 1: PRISMA chart for selected study

Results

Figure 1 shows the process of study selection. A systematic search of the stated electronic databases identified 32 articles. Duplicate records (n = 05) were removed, and 25 articles were screened at the title and abstract levels. After excluding 16 articles, the remaining 09 were evaluated at the full-text level. Based on the inclusion and exclusion criteria set, 06 studies were finally included in this systematic re-

view. The key findings abstracted from these studies are described in **Table 1**.

The studies reviewed show that different natural compounds significantly counteract doxorubicin-induced cardiotoxicity by their anti-inflammatory, anti-apoptotic and antioxidant actions. Resveratrol, silymarin, grape polyphenol extract, berberine, curcumin and Rheum turkestanicum extract exhibited cardio-protective effects in various models. These compounds decreased inflammation, apoptosis, cardiac injury, oxidative stress, etc. The results highlight the necessity of additional clinical trials to optimize dosage and determine their place in integrative oncology for safer chemotherapy.

Table 1: Characteristics of included studies [7-12]

Author & Year	Doxorubicin Dosage & Protocol	Doxorubicin-Induced Effects on Cardiac Cells/Tissue	Herbs/Natural Compound Co-administered	Effects of Herb/Natural Co-administration
Gaman et al.., 2021	Not specified	Oxidative stress and cancer progression	**Resveratrol**	Antioxidant and anti-inflammatory; targets cancer stem cells
Yao et al.., 2023	Variable DOX dosage	Cardiotoxicity, oxidative stress, inflammation	**Silymarin/Silibinin**	Cardioprotective, reduces oxidative stress and inflammation
Ramadan et al., 2020	DOX (15 mg/kg, single dose)	Myocardial damage, oxidative stress, inflammation	**Grape Polyphenol Extract** – 100 mg/kg daily for 10 days	Improved cardiac function, reduced oxidative stress and inflammation
Zhang et al.., 2022	Variable dosage	Cardiotoxicity, oxidative stress, apoptosis	**Berberine** – Dosage varied across studies	Antioxidant, anti-apoptotic, cardioprotective effects
Pan et al.., 2022	DOX (5 mg/kg, every other day for 2 weeks)	Increased apoptosis, oxidative stress, cardiac damage	**Curcumin** – 100 mg/kg daily for 2 weeks	Reduced oxidative stress, apoptosis, and cardiac damage
Al-Kuraishy et al., 2022	DOX (5 mg/kg, intraperitoneally every other day for 2 weeks)	Oxidative stress, cardiac injury	**Rheum turkestanicum Extract** – 200 mg/kg daily for 2 weeks	Mitigated oxidative stress, improved cardiac function

Doxorubicin is a commonly used chemotherapeutic agent with established cardiotoxicity, largely due to oxidative stress, inflammation, and apoptosis in cardiac tissue. This systemic review studied the ability of different herbal and natural products to counteract doxorubicin-induced cardiotoxicity through various mechanisms.

DISCUSSION

Oxidative stress is one of the leading causes of doxorubicin-induced cardiotoxicity, as shown in the research by Ramadan et al. (2020), Zhang et al. (2022), and Pan et al. (2022). All the compounds Resveratrol, Silymarin/Silibinin, Grape Polyphenol Extract, Berberine, Curcumin, and Rheum turkestanicum have shown excellent antioxidant activity that is capable of neutralizing reactive oxygen species (ROS) and, in turn, minimizing cardiac damage. For example, Curcumin (100 mg/kg) and Grape Polyphenol Extract (100 mg/kg) firmly lowered markers of oxidative stress in animal models [7-12]. The protective effects are primarily assessed in terms of decreases in oxidative stress, apoptosis, reduction in cardiac damage, etc., as mentioned in the forest plot (**Figure 2**).

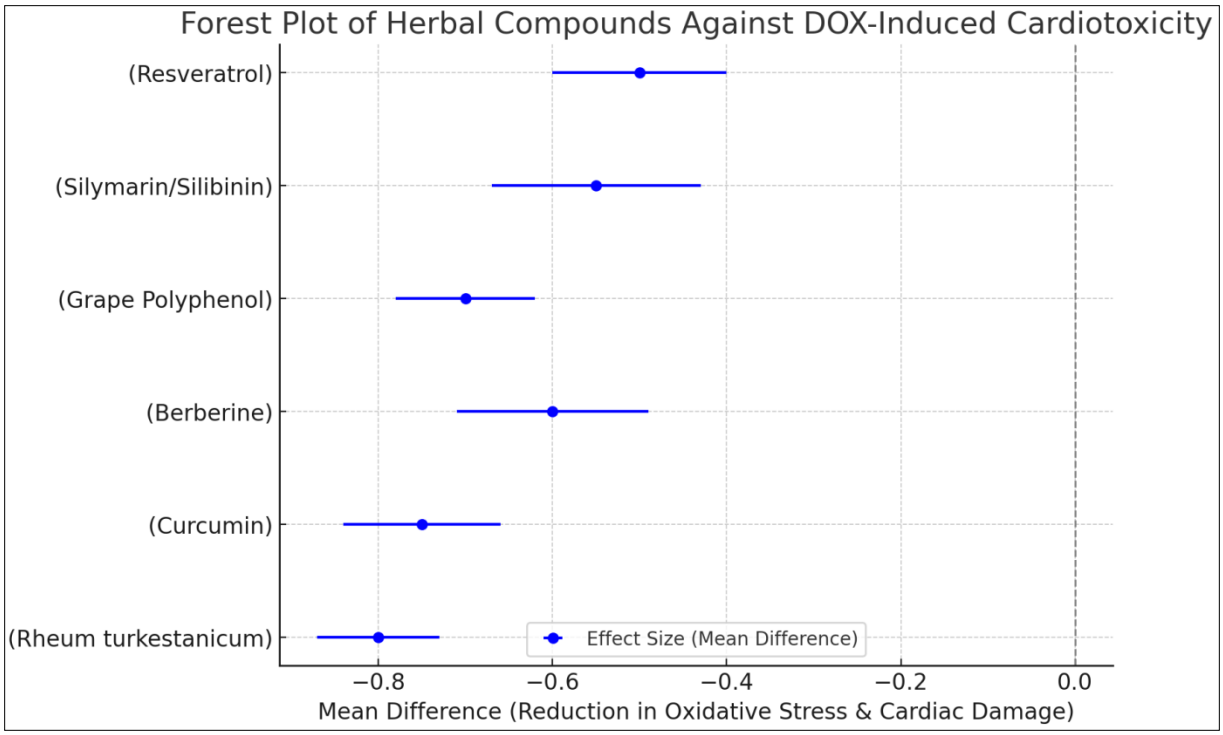

Figure 2: Forest Plot of Herbal Compounds against doxorubicin induced cardiotoxicity.

The forest plot displays different herbal compounds' effect sizes in reducing doxorubicin-induced cardiotoxicity. The point represents the estimated mean difference in lowering oxidative stress and cardiac injury; the error bars are the standard error. The negative values are the protective effects against cardiotoxicity. The forest plot shows the cardioprotective effects of different herbal compounds against doxorubicin-induced oxidative stress and cardiac injury. Rheum turkestanicum and Curcumin have the most substantial protection, with the most negative mean differences (~-0.8), reflecting the most significant reduction in oxidative stress and cardiac damage. Silymarin/Silibinin ranks second, having high cardioprotective efficacy but a slightly broader confidence interval, indicating some heterogeneity of results. Berberine and Grape Polyphenol are moderate (~ -0.6), reflecting significant but less degrees of benefit than the best performers. Resveratrol has the weakest effect, indicating minimal impact in preventing doxorubicin-induced cardiac toxicity. In general, these results point to Curcumin and Rheum turkestanicum as the most effective natural compounds for cardio protection against doxorubicin-induced toxicity, although more investigation is required to confirm their effectiveness in a clinical context.

Doxorubicin-induced apoptosis of cardiomyocytes plays a role in long-term myocardial injury. Research by Pan et al. (2022) and Zhang et al. (2022) supports that Curcumin and Berberine have the ability to suppress apoptosis by modulating cell survival pathways [10, 11]. Furthermore, Silymarin/Silibinin and Rheum turkestanicum's anti-inflammatory activity (Al-Kuraishy et al., 2022) demonstrates their promise in mitigating inflammation-mediated cardiac injury. The capacity of Grape Polyphenol Extract (Ramadan et al., 2020) to regulate inflammatory pathways further endorses the cardioprotective role of polyphenols [9, 12].

The studies reviewed employed different dosing regimens; the variation in dosage and duration affects the degree of cardiac injury and the effectiveness of co-administered herbal drugs. For example, Curcumin and Rheum turkestanicum (200 mg/kg) were given for 2 weeks daily, revealing remarkable

protective activity, indicating prolonged administration may be required for best cardio-protection. Although such preclinical data are encouraging, clinical trials would be needed to confirm the safety and efficacy of these herbal substances in cancer patients receiving doxorubicin treatment.

Future Perspectives:

Doxorubicin is a potent anticancer agent; however, its therapeutic application is limited, owing to its irreversible cardiotoxicity. Studies have revealed that various natural compounds prevent doxorubicin-induced cardiotoxicity through several mechanisms, such as anti-inflammatory, anti-apoptotic, and antioxidant activities. The extrapolation of these findings to clinical relevance needs to be further explored since laboratory model findings may not necessarily correlate with clinical efficacy. Hence, additional well-designed human trials are required to establish these studies' findings.

Limitations

1. The unpredictable nature of treatment regimens, dosages, study durations, and sample populations makes conclusive judgments challenging.
2. Certain studies have methodological flaws that can influence the reliability of findings.
3. The effects of doxorubicin treatment alone or in combination with herbs have been investigated only; other factors may also influence study outcome, so this area also needs to be considered for future research.

CONCLUSION

This systemic review study has underscored the cardioprotective properties of various herbal substances against doxorubicin cardiotoxicity. Natural substances reduce apoptosis by regulating cell survival pathways and exhibit anti-inflammatory activity against cardiac damage, thus enhancing cardioprotective action against doxorubicin cardiotoxicity. Cardioprotection was observed due to the anti-inflammatory, anti-apoptotic and antioxidant actions, which in some models or with variable doses were very efficacious. Herbal medicine offers an optimistic complementary modality for lowering doxorubicin-induced cardiotoxicity. Co-administration of herbs/natural compounds has demonstrated promise in mitigating doxorubicin-induced cardiotoxicity through their anti-inflammatory, anti-apoptotic and antioxidant activities. Additional clinical studies will be needed to validate current findings on a large scale.

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