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Review Article

Phytopharmacological Review of Grewia Hirsuta with Emphasis on its Cardioprotective Activity

Aditi Malkar*, Karna Khavane, Aditi Mishra

Dr. Vedprakash Patil Pharmacy College Aurangabad

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with heart failure being a major contributor. Among the various factors leading to cardiac dysfunction, drug-induced cardiotoxicity is a growing concern, particularly in cancer patients undergoing chemotherapy. The growing interest in natural products as cardioprotective agents has led to the exploration of phytoconstituents with antioxidant, anti-inflammatory, and cytoprotective properties. Grewia hirsuta, a medicinal plant belonging to the Malvaceae family, has been traditionally used in ethnomedicine for its diverse pharmacological properties. Despite these traditional claims, its potential role in cardioprotection remains largely unexplored. Given the strong link between oxidative stress and DOX-induced cardiotoxicity, we hypothesize that the hydroalcoholic extract of Grewia hirsuta leaves may exhibit significant cardioprotective effects through its antioxidant and anti-apoptotic mechanisms. By exploring the protective mechanisms of Grewia hirsuta, this research aims to provide a scientific foundation for its potential use as an adjunct therapy in cancer patients undergoing DOX treatment. This study, therefore, holds significant promise in bridging the gap between traditional medicine and modern pharmacology, offering a new paradigm in the management of drug-induced cardiac dysfunction. The purpose of this review is to examine how Grewia hirsuta leaf extract protects mouse models against DOX-induced cardiotoxicity. A thorough methodology that includes hemodynamic evaluations, biochemical indicators of inflammation and oxidative stress, histopathological analysis, and network pharmacology will be used to clarify the mechanism underlying its cardioprotective effects. Additionally, in vitro and in silico research will be used to pinpoint important bioactive substances and how they interact with molecular targets linked to DOX-induced cardiotoxicity.

***Corresponding Author:** Aditi Malkar
Address: *Dr. Vedprakash Patil Pharmacy College Aurangabad*
Email : aditimalkar15@gmail.com

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INTRODUCTION

The Human Heart: Structure and Function

Anatomy of the Heart

As the main pump of the circulatory system, the heart is a dynamic organ that enables the body to continuously receive oxygen and nutrients while also removing carbon dioxide and waste products from metabolism. Situated between the lungs in the mediastinum, the heart weighs between 250 and 350 grams and is about the size of a clenched fist. It rests on the diaphragm. A double-layered fibroserous sac called the pericardium encloses it. The serous pericardium inside lowers friction through pericardial fluid, while the outer fibrous layer offers structural support. In 2012, Ellis. The anatomical integrity of these components ensures that the heart maintains efficient pumping and conduction. In pathological conditions like hypertrophy, cardiomyopathy, or ischemic remodeling, alterations in structure directly impair function, making anatomical understanding critical in the context of cardioprotective research. (Anderson et al., 2004; Ellis, 2012; Mori et al., 2015)

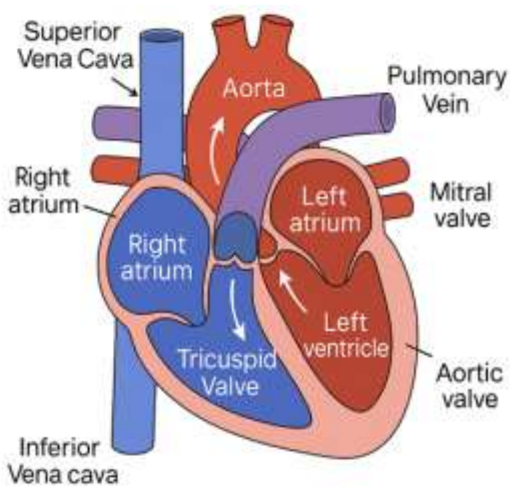

Figure 1: Anatomy of human heart

Physiology: Cardiac Cycle and Hemodynamic

The cardiac cycle is the sequence of mechanical and electrical events that repeat with every heartbeat, ensuring the coordinated contraction and relaxation of the atria and ventricles. The average heart beats about 60–100 times per minute at rest, completing this cycle efficiently and rhythmically. Each cycle consists of two primary phases: systole (contraction) and diastole (relaxation). These phases are subdivided further into isovolumetric contraction, ejection, isovolumetric relaxation, and rapid and reduced filling phases. (Kemp and Conte, 2012; Tsutsui et al., 2011)

Global and Indian Burden of CVDs:

Globally, cardiovascular diseases (CVDs) constitute the primary cause of death and a significant contributor to disability. Over the past two decades, the global burden of CVD has risen in absolute numbers even as age-adjusted rates have declined. In India, CVD burden has been rising rapidly with an epidemiological shift from infectious to non-communicable diseases. With almost one-third of all deaths coming from CVDs, they continue to be the leading cause of death worldwide. With an expected 12.1 million deaths from CVD in 1990, 18.6 million in 2019, and about 19.9 million by 2021, the number of deaths worldwide has been gradually rising. The main causes of this increase in overall mortality are aging and population expansion. The global prevalence of CVD (number of people living with cardiovascular diseases) has grown enormously over the past 20 years. In 1990 there were about 271 million people with CVD; by 2019 this had nearly doubled to 523 million prevalent cases worldwide. CVD overwhelmingly affects older adults globally, but not exclusively so. Approximately three-quarters of global CVD deaths occur in people aged 60 or above, yet a significant fraction are "premature" (before age

70), particularly in developing regions. A striking aspect of India's CVD epidemic is its premature nature. A large proportion of cardiovascular deaths in India occur at younger ages compared to higher-income countries. It is important to note that India's CVD burden varies across states and regions. Historically, more economically advanced states (and urban areas) had higher rates of heart disease.

Major Types of Cardiovascular Diseases:

1. Ischemic Heart Disease (IHD): IHD is typified by decreased blood flow to the heart, which is typically brought on by coronary artery atherosclerosis. Clinically, it shows up as myocardial infarction (STEMI and NSTEMI), unstable angina, and stable angina. It continues to be the world's leading cause of cardiac death.

2. Hypertensive Heart Disease: Chronic elevation of blood pressure leads to increased left ventricular workload, resulting in concentric hypertrophy. Over time, this causes stiffening of the ventricle, impaired relaxation, and ultimately heart failure with preserved ejection fraction (HFpEF). It also increases the risk of arrhythmias and sudden cardiac death.(MURPHY, 1947)

3. Cardiomyopathies: Cardiomyopathies are intrinsic myocardial disorders not caused by ischemia or valvular disease. Dilated cardiomyopathy (DCM) involves ventricular dilation and systolic dysfunction. Genetic testing is often necessary for familial forms.(Chan et al., 2018; Edwards, 1987; Nihoyannopoulos and Elliott, 2018)

4. Valvular Heart Disease (VHD): VHD results from stenosis or regurgitation of the cardiac valves. Rheumatic fever remains a major cause of mitral and aortic valve damage in developing countries. VHD can lead to heart failure, arrhythmias, and embolic events.(Kemp and Conte, 2012; Maganti et al., 2010)

5.Heart Failure: This condition represents a final common pathway for many cardiac diseases. Based on ejection fraction, it is classified into HFrEF (EF $<$ 40%), HFpEF (EF $\geq$ 50%), and HFmrEF (EF 41–49%). Symptoms include fatigue, dyspnea, and edema due to impaired cardiac output and fluid overload.(Tsutsui et al., 2011)

6. Arrhythmias: Electrical disturbances include bradyarrhythmias (e.g., sick sinus syndrome, AV block) and tachyarrhythmias (e.g., atrial fibrillation, SVT, VT). These may arise from structural abnormalities, electrolyte disturbances, or primary conduction disorders.(Kingma et al., 2023; Raines, 2023)

7.Congenital Heart Disease: These are structural defects present from birth, such as atrial septal defect (ASD), ventricular septal defect (VSD), Tetralogy of Fallot, and transposition of the great arteries. Early surgical intervention is often required.(Newman, 2005; Schleifer and Srivathsan, 2013)

8. Inflammatory and Infective Disorders: Conditions like myocarditis, pericarditis, and endocarditis result from infections or autoimmune reactions. Rheumatic heart disease, a sequela of streptococcal infection, remains prevalent in parts of India.(Calabrese et al., 2003; Maganti et al., 2010)

Diagnostic Markers and Tools in Cardiac Diseases:

Accurate and early diagnosis is critical for effective management and treatment of cardiac diseases. With the increasing global burden of cardiovascular diseases (CVDs), the integration of various diagnostic modalities has revolutionized the ability of clinicians to identify, monitor, and manage cardiac dysfunction. The foundation of the first cardiac evaluation is still electrocardiography (ECG). It is a non-invasive, widely available, and reasonably priced diagnostic technique that continuously logs the heart's electrical activity. Heart rate, rhythm, axis deviation, chamber enlargement, myocardial ischemia or infarction, conduction abnormalities, and electrolyte imbalances are all important information that can be obtained from the ECG. Hemodynamic monitoring provides essential data about the function and performance of the cardiovascular system, especially in critically ill patients. It involves assessment of blood pressure, cardiac output, systemic vascular resistance, and intracardiac pressures. Serum biomarkers play a vital role in diagnosing myocardial injury, stratifying risk, and monitoring response to therapy. Oxidative stress has emerged as a central player in the pathogenesis of numerous cardiac disorders

Plant Profile:

- **Biological source**: It is leaves obatined from the plant, *Grewia hirsuta* Vahl
- **Family:** Malvaceae

Taxonomy:

- **Kingdom:** Plantae
- **Phylum:** Tracheophytes
- **Class:** Eudicots
- **Order:** Malvales
- **Family:** Malvaceae
- **Genus:** *Grewia*
- **Species:** *hirsuta*

Figure 2: ***Grewia hirsuta*** **Vahl**

Common Name:

- Hindi: Kakarundah,
- Kannada: Udipe,
- Sanskrit: Gudasarkara,
- Marathi: Govli,
- Tamil: Kalunnu, Tavidu, Tavadu, Ttavuttai
- Telugu: Chimachipuru, Jibilike, Chitti jana

Morphology and Occurrence:

A shrub or small tree, Nagbala Crossberry has coarse, gray-brown, hairy branchlets. Tomentose leaves have stalks that are 2-3 mm long. Lance-shaped leaves are 6–14 cm in length and 2–3.5 cm in width. They are velvety, leathery, and turn black-brown when dried. Lateral veins can reach half the length of the leaf blade. There are four to five pairs of lateral veins, with a narrow, shallowly heart-shaped base, toothed margins, and long, pointy, or rarely blunt tips. White flowers are borne in cymes 1-5 per leaf axil, 3- or 4-flowered. Stalk of the cyme is 3-7 mm, velvety. Flower stalk is 3-5 mm, velvety. Bracts are lance-shaped, 3-4 mm. Sepals are narrowly lance-shaped, 6-7 × 1.5 mm. Petals are narrowly ovate, about 3 × 1.5 mm. Stamens are 4-5 mm. Style is longer than stamens, stigma 4-lobed. Drupe is globose or 2-lobed, sparsely coarsely hairy; drupelets 2 per lobe. Flowering: June-July.

Distribution:

Global Distribution: India, Bangladesh and Sri Lanka

Indian Distribution: State - Kerala, District/s: Palakkad, Idukki, Wayanad

Chemical Constituents:

Grewia hirsuta is rich in a diverse array of bioactive phytochemicals across different parts of the plant (leaves, roots, fruits, and whole plant). Prominent secondary metabolites include flavonoids (e.g., quercetin, kaempferol), phenolic compounds (e.g., gallic acid, caffeic acid), tannins, alkaloids, saponins, glycosides, coumarins, steroids, terpenoids, and reducing sugars. Quantitative studies revealed total phenolic contents ranging from 3.6–28.9 mg/100 mg, and total flavonoids up to 15.5–18.4 mg/100 mg, contributing to potent antioxidant activities. Identified active constituents include (4Z,12Z)-cyclopentadeca-4,12-dienone, which demonstrated strong antidiabetic potential in molecular docking studies, as well as β-sitosterol, sesquiterpenes, α-curcumene, linoleic acid, oleic acid, and myristic acid. FTIR, HPTLC, HPLC, and GC-MS analyses confirmed the presence of various bioactive functional groups and marker compounds. Additionally, the plant fibers contain high levels of cellulose (59–62%), lignin, and hemicellulose, making them suitable for eco-friendly industrial applications.

Traditional / Ethno medicinal Uses:

Grewia hirsuta holds a prominent place in traditional medicine systems, especially Ayurveda, Siddha, and folk medicine in India and Southeast Asia. It is widely used for treating fevers, inflammation, cough, asthma, tuberculosis, diabetes, liver disorders, diarrhea, gastric ulcers, rheumatism, pain, infertility, worm infestations, and as a galactagogue. The root, known as Nagbala, is traditionally employed in Rasayana therapy and is a component of classical formulations like Dashmularishta. Paste formulations are applied externally to treat abscesses and skin infections, while decoctions and powders are administered orally for antipyretic, hepatoprotective, neuroprotective, and digestive ailments. Tribal communities also use the leaves for treating body pain, and the fruits are consumed for their nutritional and medicinal value. Modern pharmacological studies that show the plant's anti-inflammatory, analgesic, hepatoprotective, anti-ulcer, antidiabetic, antimicrobial, antioxidant, and nootropic qualities are progressively corroborating these traditional claims, bridging the gap between traditional knowledge and current scientific validation.

Pharmacological Study Reported:

1.Ashana Ema et al. conducted a study titled *"Evaluation of Antiproliferative Effect of Grewia hirsuta on HepG2 Cell Lines"*, focusing on the antioxidant potential and antiproliferative activity of methanolic extracts of *Grewia hirsuta*. The primary objective was to assess the plant's cytotoxic potential against liver cancer cells and to evaluate its free radical scavenging ability through various in vitro assays. To achieve this, the researchers used methanol extracts of *Grewia hirsuta* leaves and subjected them to phytochemical screening, antioxidant assays (DPPH, hydroxyl radical scavenging, phosphomolybdenum reduction, metal chelating), and cytotoxicity analysis using the MTT assay on HepG2 cell lines. The study concluded that *Grewia hirsuta* is a promising source of natural antioxidants and exhibits significant antiproliferative effects, making it a potential candidate for further mechanistic and therapeutic studies in cancer research and oxidative stress-related disorders. (Ema et al., 2013)

2.Sunil Kumar et al. conducted a comprehensive review titled *"Traditional uses, phytochemistry, quality control and biological activities of genus Grewia,"* with the aim of compiling systematic information on the traditional uses, nutritional values, chemical constituents, and pharmacological activities of species within the *Grewia* genus, including *Grewia hirsuta*. The authors gathered data from extensive scientific databases and grey literature to explore the medicinal potential of about 27 species, emphasizing the underexplored phytochemistry of many, including *G. hirsuta*. The review highlights the traditional medicinal use of *Grewia hirsuta* (notably the variety *helicterifolia*) for The study concluded that the wide-ranging traditional applications, supported by rich phytochemistry and notable pharmacological activities like anti-inflammatory, antidiabetic, antimicrobial, hepatoprotective, and neuroprotective effects, validate the continued ethnomedicinal relevance of *Grewia* species. To fully realize the medicinal potential of lesser-known species like G. hirsuta, further targeted research is necessary. (Kumar and others, 2022).

3.Chikkamath et al. conducted a study titled *"Antioxidant and Cholinesterase Inhibitory Activity of Grewia hirsuta Vahl. Leaves"*, focusing on validating the traditional use of *Grewia hirsuta* as a nerve tonic and cognitive enhancer by scientifically evaluating its antioxidant and anticholinesterase properties. The objective was to establish a correlation between the plant's ethnomedicinal applications and its in vitro pharmacological activities. The study concluded that *Grewia hirsuta* possesses significant antioxidant and cholinesterase inhibitory activities, supporting its traditional use as a nootropic and neuroprotective agent, with potential as a safer herbal alternative for treating neurodegenerative disorders such as Alzheimer's disease. (Chikkamath et al., 2024)

Need of study:

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with heart failure being a major contributor. Among the various factors leading to cardiac dysfunction, drug-induced cardiotoxicity is a growing concern, particularly in cancer patients undergoing chemotherapy. One of the most effective and widely used chemotherapeutic agents, doxorubicin (DOX), is known for its potent antineoplastic activity against a wide range of malignancies, including breast cancer, leukemia, and lymphomas. However, despite its therapeutic benefits, the clinical application of DOX is severely limited due to its dose-dependent cardiotoxicity, which can lead to irreversible cardiac dysfunction and heart failure. The underlying mechanisms of DOX-induced cardiotoxicity involve oxidative stress, mitochondrial dysfunction, lipid peroxidation, inflammatory responses, and apoptosis of cardiomyocytes. These adverse effects not only compromise the quality of life of cancer survivors but also create significant challenges in cancer therapy by limiting the optimal dosing and long-term use of DOX. Despite extensive research efforts, there is still no FDA-approved cardioprotective agent specifically designed to prevent or mitigate DOX-induced cardiac damage, highlighting the urgent need for novel and effective therapeutic interventions.

In recent years, the exploration of natural products as potential cardioprotective agents has gained significant attention due to their multi-targeted pharmacological actions, favorable safety profiles, and potential to offer complementary therapeutic benefits alongside conventional treatments. Several plant-derived bioactive compounds have demonstrated promising cardioprotective effects by modulating oxidative stress, inflammatory pathways, mitochondrial dysfunction, and apoptotic signaling. Among the various medicinal plants with potential therapeutic benefits, *Grewia hirsuta*, a member of the Malvaceae family, has been traditionally used in ethnomedicine for its diverse pharmacological activities, including antioxidant, anti-inflammatory, and cytoprotective properties. However, despite these traditional claims, its cardioprotective potential has not been scientifically explored. Given the strong link between oxidative stress and DOX-induced cardiotoxicity, it is hypothesized that the hydroalcoholic extract of *Grewia hirsuta* leaves may exert significant cardioprotective effects through its antioxidant, anti-inflammatory, and anti-apoptotic mechanisms.

Research gap:

By exploring the cardioprotective potential of *Grewia hirsuta*, the findings of this research could contribute to the development of novel plant-derived therapies aimed at mitigating chemotherapy-induced cardiac complications. This study not only has the potential to impact the field of cardioprotection but also offers broader implications for integrative medicine, where natural products are increasingly being recognized as valuable therapeutic agents. If successful, the identification of *Grewia hirsuta* as a cardioprotective agent could pave the way for future clinical trials and translational research aimed at incorporating natural compounds into mainstream oncology and cardiology practice.

CONCLUSION:

Grewia hirsuta is a traditionally important medicinal plant rich in diverse phytoconstituents such as flavonoids (e.g., quercetin, kaempferol), phenolic compounds (e.g., gallic acid, caffeic acid), tannins, alkaloids, saponins, glycosides, coumarins, steroids, terpenoids, and reducing sugars, many of which are known to exert antioxidant, anti-inflammatory and cardioprotective effects relevant to heart health. Thus, the extract from Grewia hirsuta shows great therapeutic potential for reducing DOX-induced heart damage, confirming its traditional use and providing a scientific basis for its potential future development as an adjuvant or independent cardioprotective drug. To completely explore its medicinal potential, more research is needed.

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