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A Comprehensive Review On Terminalia Arjuna And Crataegus Spp. (Hawthorn): Cardioprotective Phytotherapeutics For Cardiovascular Health.

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Abstract: As supplemental treatments for cardiovascular illness, herbal cardioprotective substances including terminalia arjuna (Arjuna) and Crataegus spp. (Hawthorn) have drawn more and more scientific interest. Rich in triterpenoids, flavonoids, and tannins, arjuna has long been used to treat angina and ischemic heart disease because of its antioxidant, anti-ischemic, lipid-modulating, and myocardial-protective properties. Stronger data from standardized extract studies suggests that hawthorn includes flavonoids and oligomeric procyanidins that improve endothelial function, increase exercise tolerance , and include vasodilation in mild-to-moderate chronic heart failure .The dearth of large head-to-head randomized studies, preparation variation and inadequate long-term safety data remain significant constraints, despite the fact that both botanicals are generally well tolerated and have potential complimentary processes, suggesting synergistic application in cardiovascular therapy. All things considered, Arjun and hawthorn are potential phytotherapeutic agents that need more systematic, extensive clinical research to confirm their safety, effectiveness, and ideal combination for use in contemporary cardiovascular care.

Index Terms **-** Terminalia arjuna; Hawthorn; Cardiovascular health; Antioxidant activity; Synergistic therapy; Triterpenoids, Flavonoids, Phytotherapy, Ischemic Heart Disease, Endothelial Function, Anti-inflammatory action, Polyphenols

Introduction Since cardiovascular disease (CVD) remains a leading cause of morbidity and mortality globally, more focus is being placed on complementary and alternative therapy approaches that may enhance cardiovascular health. Of these, the herbal remedies prepared from arjuna (terminalia arjuna) and Hawthorn (Crataegus spp.) have garnered attention due to their historical use in traditional medicine and possible therapeutic advantages. Hawthorn and arjuna both have been shown to protect the heart, and number of studies suggest that they may be helpful in treating different heart problems.[6]

Because of its capacity to enhance heart function, lower blood pressure, and promote general cardiovascular health, Arjuna bark has been utilized in Ayurvedic medicine for many generations.[7] Its active ingredients , including flavonoids and tannins, are believed to support its cardioprotective mechanisms through their antioxidant and anti-inflammatory qualities.[8] In a similar vein, hawthorn has been used for any years in herbal

medicine to treat heart-related ailments ,and there is proof that it can increase cardiac output and reduce the symptoms to trat heart failure. [6] Flavonoids and oligomeric proanthocyanidins, two of hawthorn's active ingredients ,are thought to have vasodilatory and coronary blood flow enhancing qualities.[9]

Not with standing the encouraging results, there are still obstacles and restrictions in the field of research on these natural remedies. The development of the standardized medicinal regimens is severely hampered by the methodological flaws in clinical studies, variations in herbal preparations and dose, an regulatory obstacles. [10] Additionally, more research is required to completely comprehend Arjuna and Hawthorn's potential function in cardiovascular health due to knowledge gaps surrounding their long-term safety and effectiveness.[11]

With an emphasis on their mechanisms of action, clinical efficacy, and the need for more thorough study in this area, this literature review to give a thorough summary of the therapeutic qualities of hawthorn and arjuna bark in the treatment of cardiovascular disease.[12]

Background of cardiovascular disease:

Often named the "silent killer'', hypertension is an important contributor to of cardiovascular diseases globally. Around the world, its prevalence grows at an alarming pace.[12] Atherosclerotic plaque is triggered by a variety of risk actors ,like diabetes mellitus, dyslipidemia , hypertension, obesity, and cigarette smoking.[13]

The high cost of conventional treatment , the prevalence of chronic diseases , a general desire for well beings, and a sense that herbal remedies are safer alternatives are the primary driver of the global rise in the use of herbal remedies, with sales annually exceeding US $60 billion.[14] For the cardioprotective qualities , Terminalia arjuna and Crataegus spp. (Hawthorn) stands out among natura treatments. Triterpenoids, flavonoids, and tannins present in arjuna, and has been used for decades in Ayurveda, offer to strengthen the cardiac system, maintain blood pressure, reduce cholesterol and stop arrythmias.

Rich in flavonoids and oligomeric proanthocyanidins, hawthorn is utilized frequently across European and Chinese medicine. It stimulates vasodilation, better coronary circulation, reduced arterial stiffness, and the relief to heart failure symptoms.[7] While having lipid-modulating, anti-inflammatory, and antioxidant properties, both agents possess different mechanisms and therapeutic profiles. Therefore, it is beneficial to analyze Arjuna and Hawthorn to help to obtain statistics, emphasize beneficial features, and research probable synergistic usage in cardiovascular therapeutic.[8]

Natural Treatments' Significance for Cardiovascular Health

For a number of reasons, natural therapies have drawn a lot of interest when it comes to cardiovascular health:

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1.Increasing Prevalence of Cardiovascular Diseases: As the prevalence of CVDs rises over the world, there is an urgent need for efficient treatment alternatives. An alternate or supplementary strategy to traditional therapies is provided by natural remedies.[14]

2.Cost-Effectiveness: Since natural medicine can be less expensive than prescription drugs, especially in areas with poor access to healthcare, many people look for them.[13]

3.Perception of safety: People are more interested in using herbal medicines to treat medical ailments since they are thought to be safer than synthetic pharmaceuticals.[1]

4.Holistic Approach: Natural therapies usually support a holistic approach to health, which addresses not only the signs and symptoms of illnesses but also encourages lifestyle changes and general well-being.[15]

5.Supporting Evidence: A growing body research demonstrates the effectiveness of some natural treatments in controlling cardiovascular health, including their capacity to lower blood pressure, improve lipid profiles, and strengthen heart function.[16]

Overview and Therapeutic Benefits of Arjuna Bark Native to the Indian subcontinent, Terminalia arjuna (Arjuna) is a deciduous tree whose stem bark has been used as a cardiotonic for generations. Its cardioprotective properties—antioxidant and anti-ischemic activity, enhancement of myocardial function, lipid-modulating effects, and possible help in chronic stable angina, ischemic heart disease, and heart failure-related symptoms—are the main focus of current pharmacological and clinical research.[17]

Arjuna bark: Overview and therapeutic Benefits

Traditional Medicine's Historical Use:

In the field of Ayurvedic medicine, Arjuna has a long history. It has been used for many years to improve cardiac health and treat a range of cardiovascular conditions.[18] The bark of the arjuna tree has long been used for its many medicinal benefits, especially in enhancing heart function and controlling high blood pressure.[19]

1.Applications of Ayurveda: Arjuna is considered a cardiotonic plant in ayurveda, indicating its potential effectiveness in strengthening the heart muscle and enhancing its performance. It has been used to treat ailments like blood pressure, angina, and heart failure.[20]

2.Cultural Significance: The use of Arjuna in conventional medicine demonstrates a deep cultural understanding of phyto-therapeutic treatments. Because of its cardioprotective qualities, it has been incorporated into a variety of medicinal treatments and is commonly recommended by Ayurvedic practitioners.[21]

Fig.1: Arjuna[39]

Active Compounds and Mechanism of action

Active Compounds: Flavonoids, tannins, and triterpenoids are only a few of the many bioactive substances found in arjuna bark that contribute to its therapeutic effectiveness.[22] These ingredients are said toto have cardioprotective, anti-inflammatory, and antioxidant properties.[23]

Mechanism of action: Arjuna is valuable tool in treatment of cardiovascular disease because of the ways in which it produces its therapeutic effects, which include improving lipid profiles, reducing oxidative stress, regulating blood pressure, and strengthening the heart.[24] In conclusion, Arjuna's historical use in conventional medicine emphasizes its value as a natural remedy with potential advantages of cardiovascular health, a claim supported by a growing body of research.[18]

Clinical studies and Efficacy

Stable Angina/ischemic disease: In certain cohorts , small clinical studies and systematic reviews suggest improved exercise tolerance or symptomatic benefit along with decreased angina frequency. Due to small study sizes and inconsistent extract processing, the evidence is encouraging yet consistent.[25]

Heart failure/ left ventricular dysfunction: A number of small clinical and mechanistic investigations suggest improvements in symptoms as well as positive biomarker alterations (certain functional measurements , antioxidants markers.).Larger standardized RCTs are necessary because at least one 12-week controlled add-on trail failed to demonstrate an improvement in LVEF when compared to usual therapy , indicating conflicting findings .The quality of clinical evidence is generally poor to moderate and varies depending on the outcome.[26]

Safety and tolerability: Although there is lack of comprehensive pharmacovigilance and long-term safety data trials typically indicate good short-term tolerability with few major side events. There have been reports or hypotheses of potential impacts on platelet functions and interactions with cardiovascular medications, which calls for monitoring.[13]

Comparative Analysis with Conventional Treatments

Positioning: Rather than being a replacement for evidence-based cardiovascular medications (ACE inhibitors, B Blockers, tannins, antiplatelets, SGLT 2i/ARNI when needed arjuna should be considered a complementary or adjuvant phytotherpeutic. Arjuna's human data preliminary demonstrate clinical or biomarker benefits

without strong proof concrete outcomes, whereas conventional treatments have intensive randomized trails demonstrating decreases in mortality and hospitalization.[27]

Magnitude and endpoints: No solid evidence shows superatory or comparable hard end point benefit when compared to recommended medication; effects size reported for symptom elevation or exercise tolerance are moderate and inconsistent.

Clinical consideration include: As the supervise adjunct for symptom relief in patient who are interested in phytotherapy or when standard therapy is used leaves residual symptoms; nevertheless, standardization, dosage, and possible interaction must be taken into consideration. To clarify a role, larger, standardized RCTs with phytochemical profiling and therapeutically relevant outcomes are required.[28]

Hawthorn: Overview and its therapeutic Benefits

Historical use in traditional medicine

Hawthorn is a temperate shrub/tree with therapeutic uses for its leaves, flowers and berries (genus Crataegus; usually, C.monogyna , C.laevigata, C.oxyacantha, and hybrids).[30] Cardiovascular uses (cardiotonic effects, symptomatic improvement in chronic heart failure, mild antihypertensive and anti-ischemic) as well as anti-oxidant, anti-inflammatory, lipid modifying properties documented in experimental studies are the main focus of current clinical and preclinical work.[29]

In north America, Asia and Europe, hawthorn has a long history use in folk medicine. It has historically used to cure circulatory or kidney/bladder difficulties, digestive disorders (such as diarrhea), and heart complaints ("heart tonic"). It also occur in folklore and spiritual/herbal traditions as a plant that is "heart straightening" and protective. In20th century, pharmacopieas and contemporary research abstract begins to include the plant due to clinical interest in its cardiac effects.[31]

Fig 2: Hawthorn leaves and fruits.[40]

Active compounds and its mechanism of action:

Flavonoids (quercetin, hyperoside and vitexin) and oligomeric procyanadins (OPCs) are two important bioactive groups that are present in leaves, flowers and fruits. They are link to endothelial, vasodilatory and antioxidant activities.

Triterpenoids and phenolic acids, such as Crataegus acids and their derivatives, are associated with metabolic effects and vascular relaxation.

Additional ingredients: Trace amounts of pectin, vitamin C, and different organic acids.

Positive (mild) inotropy, peripheral and coronary vasodilation (through NO and endothelial pathways) , antioxidant and anti-inflammatory properties, mild diuretic and anti-remodeling activity, modulation of peripheral vascular resistance (which can slightly lower blood pressure), and enhancement of myocardial energy utilization are some of the hypothesized mechanisms related to cardiovascular effects .Rather than summarizing a single dominating pathways, mechanistic reviews summarize multimodal activity.[32]

Clinical Studies and Efficacy

Chronic heart Failure (NYHA I–III): The strongest clinical indication for these is present. When used as adjuvant to standard care, several randomized studies and meta analyses of standardized extracts(most notably WS-1442 and LI132) shown moderate but consistent increases in quality of life , exercise tolerance /maximal workload ,and symptom scores .A moderate degree of evidence for symptomatic benefit is supported by systematic reviews , which include high quality meta-analysis and Cochrane-style evaluations .Trial safety results are encouraging, however there is little long-term pharmacovigilance.[33]

Hypertension /peripheral vascular resistance: A number of short trials and meta-analyses show that moderate hypertension can result in modest drops in both systolic and diastolic blood. pressure; the results vary depending in the population, dose, and extract standardization.[34]

Ischemic symptoms/angina/microcirculation: The evidence is not as strong as it is for heart failure; while some trials and mechanistic research point to enhanced coronary microcirculation and anti-ischemic potential, there is insufficient evidence from big RCT data for Angina.[35]

Tolerability and safety: Clinical investigations have shown that it is generally well tolerated; modest side effects, such as dizziness or gastrointestinal distress, are typically recorded. A description of significant interaction signals can be found below.[36]

Safety, Interactions and Practical considerations

Interactions: There have been reports or theories of possible interactions with cardiac medications, especially with digitalis glycosides (possible additive inotropic effects), antihypertensive (possible additive lowering blood pressure), and anticoagulant /antiplatelet medications (possible risk via effects on platelet function). Always assess concurrent medications and keep a clinical eye on them.[36]

Standardization and quality: Standardized extracts used in trials are associated with clinical benefit (WS-1442, LI132). The species, plant part, extraction technique, and active ingredients amount of over-the-counter products vary greatly; choose those with clinical evidence and established standardization.[37]

Regulatory status: In many countries, hawthorn is sold as a herbal supplement or nutraceuticals;

Certain extracts have been utilized in clinical trials, and in other nations, there are registered formulations or monographs.[30]

Comparative Analysis of Hawthorn and Arjuna bark

Botanical /Phytochemical Profile	Bark that is high in triterpenoids, saponins, tannins and phenolics these components are thought to have anti-inflammatory, antioxidant, and membrane-stabilizing property.	Fruits, flowers and leaves high in oligomeric procyanidins (OPCs) and flavonoids (vitexin, hyperoside) are known to provide endothelium protection, modest positive inotropy, and vasodilation effect.
Primary pharmacodynamic differences	More proof of lipid/anti-ischemic effects and cardiac protection (membrane stabilization, decreases ischemia-reperfusion injury) in preclinical and modest clinical trial.[18]	Greater proof of meaningful vasodilatory/antiarrhythmic effects using well studied standardized extracts (e.g., WS 1422) as well as symptomatic improvement in chronic heart failure (exercise tolerance, symptoms) from RCTs and meta analysis.[37]
Clinical evidence quality and standardization	Numerous encouraging clinical and observational studies, but smaller trials and greater variation in extract standardization; altogether, the evidence is encouraging but less reliable than the best hawthorn research	A number of higher-quality RCTs and systematic reviews employing standardized extracts (WS 1422) demonstrate a satisfactory safety profile and suggest symptomatic improvement in NYHA II patients.
Safety and interactions	Highly compatible. Although there are fewer high-quality interaction studies available, Arjuna safety data are comforting.	Well tolerate. For standardized extracts, hawthorn's interaction data (including controlled study with digoxin) indicate few clinically significant pharmacokinetic interactions; nonetheless, pharmacodynamic overlap (e.g., hypotension, inotropy) should be monitored.[38]

Dosing and Formulation	Although methods vary, standardized bark extracts are frequently used in standardized and commercial items (eg., supplement containing 250-500 mg/day. When reporting dose in review always, indicate the specific extract standardization.	Different standardized extract and daily dosages (often hundreds of milligram per day of standardized extract for 8-12+ weeks) were utilized in crataegus trials.

Synergistic effect in combination therapy

Arjuna (Terminalia arjuna)	Key constituents	triterpenoids, flavonoids, tannins, glycosides and polyphenols.
	Mechanisms	positive inotropic effect (improves contractility), increases coronary blood flow, antioxidant activity, lipid-lowering effects, mild hypotensive action via vasodilation and improved endothelial function.[13]
Hawthorn (Crataegus spp.)	Key constituents	oligomeric procyanidins (OPCs), flavonoids, vitexin derivatives, and other polyphenols.
	Mechanisms	mild positive inotropy, vasodilation (nitric oxide pathway / smooth muscle relaxation), anti-ischemic and anti-arrhythmic properties in some models, antioxidant effects, and possible improvement of exercise tolerance and symptom scores in mild-to-moderate CHF.[41]

Hawthorn (Crataegus)exhibits mild positive inotropy, vasodilation, anti-ischemic, and antioxidant effects; arjuna is mainly reported-flow enhancer, lipid-lowering and antioxidant bark extract. Both plants have independent, presumably complementary cardiovascular effects. Terminalia arjuna.

Rationale for Synergy: Hawthorn's vasodilatory and symptomatic benefits combined with Arjuna's myocardial-strengthening and lipid-modifying properties may work in concert to enhance cardiac function, lower afterload, and relieve symptoms (fatigue, dyspnea) more effectively than either one alone, although there isn't much high-quality clinical evidence to support this particular combination.[41]

Methodological Issues in Clinical Trials of Terminalia Arjuna and Cratageus spp.

1.Standardization and Phytochemical extracts are lacking

Few clinical studies report quantitative marker compounds and frequently use different species, plant parts (bark, leaves, flowers, berries), and extraction solvents. Standardized extracts like WS-1422 have been thoroughly researched for hawthorn, but arjuna experiments usually employ unrefined bark powders or decoctions that lack phytochemical profile. This discrepancy restricts comparability and reproducibility.[1]

2.Insufficient power and small sample sizes

The majority of arjuna and hawthorn trials are single-center, enroll fewer than 100 participants, and have insufficient power to detect changes in hard endpoints like hospitalization or cardiovascular mortality. In meta-analyses, this leads to type II error and exaggerated effect sizes.[3]

3.Inadequate disclosure of binding and randomization

Details about allocation concealment, random sequence generation, and placebo design are missing from a number of research. The taste and odor of herbal remedies present difficulties and raise the possibility of prejudice. There are very few hawthorn trials that used indistinguishable tablets as a double-blind placebo control.[42]

4.Brief follow-up and scant safety evaluation

The majority of research on hawthorn and arjuna last between two to sixteen weeks, which is too short to evaluate long-term effectiveness or uncommon side effects. Herb -drug interaction (e.g., arjuna with antiplatelets, hawthorn with digoxin) are still poorly understood, and pharmacovigilance data are limited.[4]

5.Relaince on surrogate endpoints

The majority of clinical trials evaluate clinical manifestations (such as the frequency of angina and the New York Heart Association classification), exercise capacity, left ventricular ejection fraction, or lipid biomarkers, instead of definitive cardiovascular outcomes. Enhancements in surrogate markers do not consistently correlate with a reduction in mortality or morbidity.[43]

6.Insuffiecient dose response studies and inconsistent dosage

Arjuna trials have documented dosage variations encompassing 500 mg of bark powder to 2-3 g/day of decoction; however, there exists a paucity of pharmacokinetic data. Trials involving hawthorn extract frequently administer dosages between 300 and 1800 mg/day, yet there is a notable absence of consistency across different trials. A limited number of studies systematically investigate varying dosages.[1]

7.External validity is limited

Hawthorn trials are primarily carried out in Europe, whereas the majority of arjuna trails are carried out in Indian Population. Uncertainty surrounds generalizability to other comorbidities, races, and contemporary treatment environments.[3]

8.Publishing prejudice and selective reporting

Negative trials are not published, whereas positive results are more likely to be. The industry frequently funds proprietary hawthorn extracts (like WS-1422), which enhances standardization but raises questions about sponsorship bias.[2]

. Constraints, in Ongoing Research.

Challenges and Limitation in Current Research

1.Heterogeneity and lack of extract standardization

Trials use variety of plant parts and species, including leaves, flowers, berries, and bark and employ extraction solvents and target marker compounds, which results in significant inter-study variability and makes accurate result pooling difficult. Standardized extracts, like hawthorn's WS-1422, are more of an exception than the rule.[44]

2. Small, methodologically variable clinical trials

A sizeable portion of research -The work on arjuna -is usually conducted as open-label studies and is usually limited to a single center. Randomization, binding, allocation concealment, and intention-to-treat analyses are frequently presented in an inconsistent manner, which increases the risk of bias and may inflate the observed effect sizes. On the other hand, meta-analyses of hawthorn often highlight the heterogeneity of the trials and the typically low quality of the data, while also pointing to small clinical benefits.[3]

3. Endpoints: surrogate and symptomatic outcomes rather than hard cardiovascular endpoints

We get biomarker levels, exercise capacity, symptom scores and surrogate physiological readouts (e.g., blood pressure lipid panels or alterations, in ejection fraction) during trials. Few well-powered studies truly focus on endpoints such as death, major adverse cardiovascular events (MACE), or hospital admissions. This scarcity makes it harder, for doctors to determine whether an intervention genuinely offers hard-outcome benefits.[3]

4.Short follow-up and limited long-term safety / pharmacovigilance data

Typically, follow-up periods last anything from a few weeks to many months There is still little data on the long-term safety and efficacy of botanicals, and there is seldom any population wide pharmacovigilance.[13]

5. Inconsistent dosing and unclear dose–response relationships

The reported dosages, preparations, and dosing schedules vary from study to trial. Reproducing results and putting them into practice remain extremely difficult in the absence of dose-finding studies and thorough phytochemical quantification.[45]

6. Species identification, adulteration and quality-control issues

Interpretation and reproducibility can be complicated by misidentifying the plant, introducing adulterants, or dealing with constantly shifting growing and harvesting conditions, such as seasonal changes, geographical peculiarities, and the various ways the, material is handled after harvest. In the meanwhile, there are significant regional and manufacturer-specific differences in the consistency of batch-level quality control and the level of oversight.[46]

7. Drug-herb interactions and interference with assays

In addition to analytical oddities like hawthorn ingredients skewing serum digoxin immunoassays, there are indications of pharmacodynamic conflicts— hawthorn may interact with medications and arjuna is believed to impact platelet function. However, these results are only marginally quantified in cohorts, creating a safety gray area whenever botanicals are used in conjunction with cardiovascular medications based on guidelines.[47]

8. Publication bias, selective reporting and commercial influence

The literature may be skewed by selective cherry-picking of results, unpublished negative studies, and modest-scale trial effects. Although industry-sponsored research on extracts may increase standardization, it also introduces commercial bias; funding sources and data exchange are still not transparent.[3]

9.Translational gaps: preclinical promise vs clinical reality

The cocktail-like nature of plant extracts, their murky bioavailability, and the conspicuous lack translational biomarker data make it difficult to actually link any particular phytochemical to patient-level outcomes, even though mechanistic and animal work illuminates a menu of heart-shielding routes—antioxidant action, anti-remodeling effects, lipid tweaks.[13]

10.Few head-to-head or additive-design trials with modern guideline therapy

Few powered trials compare arjuna to hawthorn head-to-head or examine any additional benefits they might offer in addition to the current standard regimens (ACEi/ARB/ARNI, beta-blockers, SGLT2i, statins). This lack of information translates into recommendations for physicians on how to utilize them as an adjuvant.[43]

Sources of variability in Herbal Preparation and Dosage for Terminalia arjuna (Arjuna) and Crataegus spp.(Hawthorn)

Source of variability	Description/impacts	Key findings and examples
1. Botanical identity and raw material	Phytochemical concentration is changed by species/subspecies variation, plant part used (bark vs leaf/flower), and harvest maturity. Reproducibility is limited when voucher specimens are absent.[48]	Various species and chemotypes of Terminalia and Crataegus are employed; the active phytoconstituent profiles (tannins, triterpenoids, and flavonoids) vary considerably.[49]
2. Agro-climatic and geographic factors	Levels of bioactive compounds are significantly influenced by growing circumstances and provenance.	The amount of arjunolic acid in T. arjuna bark varies by more than 100x amongst accessions, and the efficacy of t5he extract is influenced by the regional environmental circumstances.
3. Extraction method and formulation	Which phytochemicals are concentrated depends on the extraction temperature, solvent polarity, and purification. Modern and traditional extracts are very different.[50]	Triterpenoid and antioxidant concentrations vary between ethanolic and aqueous extracts. In contrast to alcohol-based extract, traditional Ksheera Paka (milk-based decoction) shows unique bioactivity.[51]
4. Standardization (or lack thereof)	Different extracts are used in different clinical investigations; variable markers and uneven quantification have an impact on dose comparability and reproducibility.	While T. arjuna lacks a consistent identifier, it is frequently standardized by arjunolic acid, arjungenin, or total tannins. Hawthorn is frequently standardized as WS®1442 (2.2% vitexin-2″-O-rhamnoside). While T. arjuna lacks a consistent identifier, it is frequently standardized by arjunolic acid, arjungenin , or total tannins. Hawthorn is frequently standardized as WS 1422 (2.2% vitexin-2″-O-rhamnoside.)

5. Dose regimens and duration	Meta-analyses and cross-trial comparisons are made more difficult by significant inter-study variance in dose and duration.	T. arjuna: 500mg extract three times a day (1–2g/day) or 4g/day bark powder; studies lasted 1–24 weeks. Crataegus: WS-1422 extract 160–1800 mg daily (usually 300–900 mg daily); usually taken for 6–8 weeks
6. Co-interventions and concomitant medicines	Confusion and possible drug-herb interactions are introduced when cardiovascular medications (ACE inhibitors, diuretics, and antiplatelets) are taken together.	Many studies do not completely control for concurrent medications, which may result in additive hypotensive/inotropic effects.

Regulatory and Standardization challenges

1.Uncertainty in classification and the regulatory environment

Herbal products for cardiovascular use, such as T. arjuna and Crataegus spp., fall under a number of regulatory categories in different countries. These include dietary supplements, traditional/herbal medicine products, and complete, medicinal products. Each of these categories has its own set of standards for quality, labeling, and supporting data. While the EU offers a simplified traditional herbal registration route (HMPC/THMPD) for long-standing use, quality and safety dossiers are required for marketing. In contrast, many products in the U.S. are marketed as dietary supplements under the DSHEA and are therefore not pre-approved for disease-treatment claims. These disparate frameworks have a direct impact on the production and reporting of clinical and quality data.[52]

2.Gaps in monograph and pharmacopeial coverage.

Cross-study comparability is facilitated by Hawthorn's strong legacy of standardized, clinically validated extracts (e.g., WS 1422) and well developed European monographs. The absence of comparable, standardized international monographs for T. Arjuna makes cross-jurisdictional quality assessment more difficult. Although Indian pharmacopeial and AYUSH guidelines are in place, analytical and marker requirements are not entirely aligned with western pharmacopeial standards.[53]

3.Raw material variability and supply-chain (GACP)

Significant variations in phytochemical profiles and marker compound levels are caused by variations in species, plant portion, harvest time, provenance, and post-harvest management. WHO/EMA advises adopting Good Agricultural and Collection Practices (GACP) to lessen this variability, however regional variations in implementation and enforcement batch-to-batch variations that compromise safety assessment and reproducibility.[54]

4.Standardization, analytical methods and marker selection

The two herbs are not consistently standardized. Clinical research on Hawthorn frequently employs quantified extracts (oligomeric procyanidin /flavonoid markers; WS 1422 is well characterized), whereas studies on T. arjuna report a variety of markers (arjunolic/arjunic acids, arjungenin, ellagitannins) and employ a combination of analytical methods (HPLC, HPTLC, fingerprinting). Reliable cross-trial comparisons of dosage, potency, and effect are hindered by the lack of agreement on validated markers and multi-component fingerprints.[55]

5. Manufacturing quality, contamination and adulteration risks (GMP)

Heavy metals, pesticides, mycotoxins, microbiological pollutants, or pharmaceutical adulteration can all contaminate herbal products. Safety signals in the literature are complicated by regulatory capacity and enforcement gaps that permit substandard or contaminated goods to enter some markets, despite the fact that national GMP criteria and WHO GMP guidance for herbal medicines set expectations for production quality and batch testing.[54]

6 Evidence thresholds ,trial design and claim translation

Regulatory pathways determine the required proof. While claims for the treatment of serious cardiovascular problems (such heart failure) require clinical trials that fulfill drug-levels standards, traditional-use registrations may accept long-standing use for non-serious purposes. Herbal drug pathways (FDA guidance) describe how to develop a herbal product as a drug, but those requirements (CMC, standardized material, adequately powdered RCTs) are expensive and rarely met by most manufacturers. Hawthorn has multiple randomized trials and systematic reviews supporting adjunctive use of chronic heart failure. This results in a

two-part body of evidence: a small number of diverse investigations versus a few well-standardized extracts trials.[3]

7. Pharmacovigilance and drug-herbs interactions monitoring

Routine monitoring of herb-drug interactions, which is crucial for cardiovascular treatments like anticoagulants and antihypertensives, is typically insufficient, and post-marketing adverse-event reporting for herbal products is weaker than for conventional therapies. This underreporting raises questions regarding the safety of using herbs in combination with prescription medications in the real world. Better reporting guidelines and proactive pharmacovigilance are required.[56]

Gaps in knowledge on long-term safety and efficacy -Terminalia arjuna (arjuna) and Crataegus spp. (Hawthorn)

1. Lack of long-term randomized data, particularly for T. arjuna

Lack of long-term randomized date. The majority of T. arjuna clinical trials are brief (weeks to months) and vary in preparation and dosage; there aren't many clear, sufficiently powered studies with years of follow-up that assess clinical cardiovascular results and safety. This makes the long-term advantages and disadvantages unclear.[17]

2.Insufficient long-term results, even for more thoroughly researched hawthorn extracts

While some studies show acceptable safety when added to conventional heart failure therapy, the evidence for hard long-term outcomes (mortality, long-term hospitalization reduction) is still inconclusive and warrants more long-term study. Standardized hawthorn extracts (e.g., WS 1422) have longer and longer trials than most botanicals.[37]

3.Limited information on infrequent, postponed, or cumulative adverse events

The sample size and exposure duration required to identify uncommon side events, cumulative toxicity (e.g., hepatic, renal), or late emergent cardiac hazards are insufficient in small studies and brief surveillance periods. True low-frequency harms are not identified in the absence of strong post-marketing surveillance and registry data.[3]

4.Long-term herb-drug interactions risk in actual polypharmacy is poorly described.

Anticoagulants, antiplatelets, statins, ACE inhibitor, beta-blockers, and antiarrhythmics are frequently prescribed to cardiovascular patients. The majority of the evidence is in the form of case reports or brief pharmacokinetic studies; there are few systematic prospective interaction studies and long-term pharmacovigilance particularly evaluating interactions (and clinically significant outcomes of interactions). This generates ambiguity for safe co-prescribing.[57]

5.Absence of data on batch variability, product quality, and long-term adherence

Consistent product quality is essential for long-term efficacy and safety. Since batch identity, marker content over time, and adherence to GACP/GMP are not reported in many lengthy trials, it is unknown if observed long-term effects—or lack thereof—are related to the botanical itself or inconsistent product quality. [17]

Conclusion

With centuries of traditional use and a growing amount of contemporary scientific evidence, Yerminalia arjuna and Crataegus spp. (hawthorn) are two of the most promising botanical therapies for cardiovascular health. While hawthorn has the best clinical evidence for enhancing symptoms, exercise tolerance, and quality of life in mild-to-moderate chronic heart failure due to its vasodilatory and endothelial-supportive properties, arjuna shows noteworthy benefits in myocardial protection, lipid modulation, and symptomatic relief in ischemic and anginal condition. The antioxidant, anti-inflammatory, and cardiotonic processes that both plants provide point to possible synergistic usage as adjuvant medicines. But there are still a lot of unanswered questions, mostly about extract standardization, long-term safety, proper dosage, and the dearth of sufficiently strong randomized controlled trials that measure precise cardiovascular endpoints. Therefore, current data supports their cautious incorporation as adjuvants rather than primary therapies, especially when used in patients already undergoing medical therapy guided by guidelines and under clinical supervision. To turn their therapeutic promise into evidence-based cardiophytotherapeutics with clearly defined clinical functions, future research involving standardized preparations, pharmacovigilance, and combination therapy studies will be essential.

Reference

1.Dwivedi, S (200a 7). Terminalia arjuna Wight & Arn.— A useful cardiovascular drug. Journal of Ethnopharmacology, 114(2), 114-129.
2.Bhargani, A., Ganguly, A., & Bhargava, K. D. (2002). Salutary effect of Terminalia arjuna in patients with severe refractory heart failure. International Journal of Cardiology, 85(2–3), 231–237
3.Pittler, M. H., & Ernst, E. (2003). Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. American Journal of Medicine, 114(8), 665–674.
4.Tauchert, M. (2002). Efficacy and safety of Crataegus extract WS® 1422 in congestive heart failure. Arab Journal of Medicinal Sciences, 5, 157–164
5.Parveen, A., Parveen, R., Parveen, S., & Ahmad, S. (2019). Challenges and guidelines for clinical trial of herbal drugs. Journal of Pharmacy & Bioallied Sciences, 11(3), 1–7.
6.Koch, E., & Malek, F. A. (2011). Standardized extracts from hawthorn leaves and flowers in the treatment of cardiovascular disorders – Preclinical and clinical studies. Planta Medica, 77, 1123–1128.
7.Jaisal, H.D., Shinde, M. E., & Avhad, A. D. (2025). A review on arjuna and hawthorn and their role in cardiovascular health. Journal of Pharmacognosy and Phytochemistry, 14(2), 502–507.
8.Wu M,Liu L, Xing Y, Yang S, Li H and Cao Y (2020). Roles and Mechanisms of Hawthorn and Its Extracts on Atherosclerosis. A Review. Font. Pharmacol. 11:118.
9.Zick, S. M., Vautaw, B. M., Gillespie, B., & Aaronson, K. D. (2009). Hawthorn Extract Randomized Blinded Chronic Heart Failure (HERB CHF) Trial. European Journal of Heart Failure, 11(10), 990–999.
10. European Medicines Agency. (2016). *Reflection paper on the regulatory guidance for the use of herbal medicinal products in the European Union*. European Medicines Agency. https://www.ema.europa.eu/en.
11.Maulik, S. K., & Talwar, K. K. (2012). Therapeutic potential of Terminalia arjuna in cardiovascular disorders. American Journal of cardiovascular Drugs, 12(3), 157–163.
12.Mills, K. T., Stefanescu, A., & He, J. (2020). The global epidemiology of hypertension. Nature Reviews Nephrology, 16(4), 223-237.
13.Ramesh, P.; Palaniappan, A. Terminalia arjuna, a Cardioprotective Herbal Medicine-Relevancy in the Modern Era of Pharmaceuticals and Green Nanomedicine —A Review. Pharmaceuticals 2023, 16, 126.
14.Rabab'ah, A. M., Yacoub, O. N. A., El-Elimat, T., Rabab'ah, M., Attarabsheh, S., Deo, S., Al-Azayzih, A., Zayed, A., Alazzam, S., & Alzoubi, K. H. (2020). The effect of hawthorn flower and leaf extract (Crataegus Spp.) on cardiac hemostasis and oxidative parameters in Sprague Dawley rats. Heliyon, 6(8), e04617.
15.Tassell, M. C., Kingston, R., Gilroy, D, Lehane, M., & A. (2010). Hawthorn (Crataegus spp.) in the treatment of cardiovascular disease. Pharmacognosy Reviews, 4(7), 32–40.
16.Patil, J., Chaudhari, M., & Gagarani, M. B. (2025). Preclinical Insights into the therapeutic Potential of Hawthorn in Hypertension Management: R Review. International Journal of Pharmaceutical Sciences, 3(6), 3879-3896.
17.Dwivedi, S., & Jauhari, R. (2020). Terminalia arjuna in cardiovascular diseases: A comprehensive review. Journal of Traditional and Complementary Medicine, 103(3), 221-227.
18.Dwivedi, S., & Chopra, D. (2014). Revisiting Terminalia arjuna: An ancient cardiovascular drug. Journal of Traditional and Complementary Medicine, 4(4), 224-231.
19.Anka, Z. M., Singh, V., Singh, G., & Gimba, S. N. (2019). The pharmacological activities of various extracts from Terminalia arjuna bark: A review, International Journal of Current Medical and Pharmaceutical Research, 5(12A), 4843-4851.
20.Kushare, S. (2022). Terminalia arjuna: An indigenous ancient drug for cardio protection. International Journal of Pharmaceutical Research and Applications, 7(1), 1271-1279.
21.Agarwal, H., Singh, B., & Kumar, A. (2021). Ayurveda's magic remedies: A review of Arjuna for the heart, Neem for purity and Neem for purity and Turmeric for life. International Journal of Herbal Medicine, 9(4), 41-45.
22.Jha, S. P., Vyas, L., & Uppalwar, S. (2020). Arjuna bark (terminalia arjuna): A comprehensive review of its pharmacological properties and therapeutic potential. International Journal of Pharmaceutical Sciences and research, 11(8), 3675-3682.
23. Wasiullah, M., Yadav, P., Maury, S., & Altamash, M. (2025). Evaluation of chemical constituents of Terminalia arjuna bark: As a cardio-protective agent. Research & Reviews: A Journal of Pharmaceutical Science, 16(1), Article 2025.
24.Nerkar, A. G., Dumbre, R. K., & Badar, S. (2023). Ethnopharmacological review of arjuna. Current Trends in Pharmacy and Pharmaceutical Chemistry, 5(1), 21-25.

25.Kaur, N., Shafiq, N., Negi, H., Pandey, A., Reddy, S., Kaur, H., Chadha, N., & Malhotra, S. (2014). Terminalia arjuna in chronic stable angina: Systematic review and meta-analysis. Cardiology Research and Practice, 2014, 281483.
26. Maulik, S. K., Wilson, V., Seth, S., Bhargava, B., Dua, P., Ramakrishnan, S., & Katiyar, C. K. (2016). Clinical efficacy of water extract of stem bark of Terminalia arjuna (Roxb. Ex DC.) Wight & Arn. In patients of chronic heart failure: A double-blind, randomized controlled trial. Phytomedicine, 23(11), 1275-1284.
27. Katsanopoulou, M., Zannas, Z., Ofrydopoulou, A., Maria, C., Krokidis, X., Lambropoulou, D. A., & Tsoupras, A. (2025). Anti-Inflammatory and Antiplatelet Interactions on PAF and ADP Pathways of NSAIDs, Analgesic and Antihypertensive Drugs for Cardioprotection—In Vitro Assessment in Human Platelets. *Medicina*, *61*(8), 1413
28. Piekarz, J. (2025). *Phytotherapy as an adjunct to the treatment of rheumatoid arthritis: A systematic review*. *Phytotherapy Research*. https://doi.org/10.1002/ptr.8384
29. Wang, J., Xiong, X., & Feng, B. (2013). Effect of Crataegus usage in cardiovascular disease prevention: An evidence-based approach. *Evidence-Based Complementary and Alternative Medicine, 2013*, Article 149363. https://doi.org/10.1155/2013/149363
30.National Center for Complementary and Integrative Health. (n.d.). *Hawthorn*. U.S. Department of Health and Human Services. https://www.nccih.nih.gov/health/hawthorn.
31.American Botanical Council. (n.d.). *Hawthorn (Crataegus spp.) in traditional medicine*. Retrieved October 19, 2025, from https://www.herbalgram.org.
32.Gheitasi I, Savari F, Akbari G, Mohammadi J, Fallahzadeh AR, Sadeghi H. Molecular Mechanisms of Hawthorn Extracts in Multiple Organs Disorders in Underlying of Diabetes: A Review. Int J Endocrinol. 2022 Jun 7;2022:2002768.
33.Pittler, M. H., Schmidt, K., & Ernst, E. (2003). Hawthorn extract for treating chronic heart failure: Meta-analysis of randomized trials. *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews*. https://www.crd.york.ac.uk/CRDWeb/.
34.Kiefer, D. (2008, January 1). Hawthorn: An herb that helps hypertension. *Clinician Reviews*. https://www.clinician.com/articles/8911-hawthorn-an-herb-that-helps-hypertension.
35.Wu M, Liu L, Xing Y, Yang S, Li H, Cao Y. Roles and Mechanisms of Hawthorn and Its Extracts on Atherosclerosis: A Review. Front Pharmacol. 2020 Feb 21;11:118. doi: 10.3389/fphar.2020.00118. PMID: 32153414; PMCID: PMC7047282.
36. Dahmer, S., & Scott, E. (2010). Health effects of hawthorn. *American Family Physician*, *81*(4), 465–468.
37. Holubarsch CJF, Colucci WS, Eha J. Benefit-Risk Assessment of Crataegus Extract WS 1442: An Evidence-Based Review. Am J Cardiovasc Drugs. 2018 Feb;18(1):25-36. doi: 10.1007/s40256-017-0249-9.
38. Dahmer, S., & Scott, E. (2010, February 15). Health effects of hawthorn. *American Family Physician*, *81*(4), 465–468. PMID: 20107582
39. Hoq, M. O. (2018). A cardio protective medicinal plant Terminalia arjuna: Evidence from traditional medicine and recent research. International Journal of Unani and Integrative Medicine, 2(2), 85–88.
40. Britannica Editors. (2025, October 19). Hawthorn. In Encyclopaedia Britannica. https://www.britannica.com/plant/hawthorn.
41. Wang, J., Xiong, X., & Feng, B. (2013). Effect of *Crataegus* usage in cardiovascular disease prevention: An evidence-based approach. *Evidence-Based Complementary and Alternative Medicine*, **2013**, 149363. https://doi.org/10.1155/2013/149363.
42. Daniele, C., Mazzanti, G., Pittler, M. H., & Ernst, E. (2008). Hawthorn (*Crataegus* spp.) extract for treating chronic heart failure. *Cochrane Database of Systematic Reviews*, 2008(1), CD005312. https://doi.org/10.1002/14651858.CD005312.
43. Holubarsch, C. J., Colucci, W. S., Eha, J., Müller-Werdan, U., & Nixdorff, U. (2000). The efficacy and safety of Crataegus extract WS 1442 in patients with heart failure: The SPICE trial. *European Journal of Heart Failure*, 2(4), 441–449. https://doi.org/10.1016/S1388-9842(00)00096-2.
44. Chawla, R., Thakur, P., Chowdhry, A., Jaiswal, S., Sharma, A., Goel, R., Sharma, J., Priyadarshi, S. S., Kumar, V., Sharma, R. K., & Arora, R. (2013). Evidence-based herbal drug standardization approach in coping with challenges of holistic management of diabetes: A dreadful lifestyle disorder of the 21st century. *Journal of Diabetes & Metabolic Disorders*, 12(1), 35. https://doi.org/10.1186/2251-6581-12-35
45. Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4, 177. https://doi.org/10.3389/fphar.2013.00177.
46. Kunle, O. F., Egharevba, H. O., & Ahmadu, P. O. (2012). Standardization of herbal medicines—a review. *International Journal of Biodiversity and Conservation*, 4(3), 101–112. https://doi.org/10.5897/IJBC11.152.

47. Dasgupta, A., Kidd, L., Poindexter, B. J., & Bick, R. J. (2010). Interference of hawthorn on serum digoxin measurements by immunoassays and pharmacodynamic interaction with digoxin. *Archives of Pathology & Laboratory Medicine*, 134(8), 1188–1192. https://doi.org/10.5858/2009-0404-OA.1
48. Ranjan, R., Singh, S., & Kumar, S. (2021). Agro-climatic zone-based identification of elite *Terminalia arjuna* accessions with respect to arjunolic acid production. *SN Applied Sciences*, 3, 246. https://doi.org/10.1007/s42452-021-04207-1.
49. Edwards, J. E., Brown, P. N., Talent, N., Dickinson, T. A., & Shipley, P. R. (2012). A review of the chemistry of the genus *Crataegus*. *Phytochemistry*, *79*, 5–26. https://doi.org/10.1016/j.phytochem.2012.04.006.
50. Meena, D. K., Sahoo, A. K., Srivastava, P. P., Sahu, N. P., Jadhav, M., Gandhi, M., Swain, H. S., Borah, S., & Das, B. K. (2021). On valorization of solvent extracts of *Terminalia arjuna* (Arjuna) upon DNA scission and free radical scavenging improves coupling responses and cognitive functions under in vitro conditions. *Scientific Reports*, 11(1), 10656. https://doi.org/10.1038/s41598-021-88710-w.
51. Dube, N., Nimgulkar, C., & Bharatraj, D. K. (2016). Validation of therapeutic anti-inflammatory potential of *Arjuna Ksheera Paka*—A traditional Ayurvedic formulation of *Terminalia arjuna*. *Journal of Traditional and Complementary Medicine*, 7(4), 414–420. https://doi.org/10.1016/j.jtcme.2016.11.006.
52. U.S. Food and Drug Administration. (2024, October 1). *Dietary supplements*. https://www.fda.gov/food/dietary-supplements.
53. European Medicines Agency. (2016). *Reflection paper on the regulatory guidance for the use of herbal medicinal products in the European Union*. European Medicines Agency.
54. World Health Organization. (2003). *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants*. World Health Organization. https://www.who.int/publications/i/item/9241546271.
55. Blumenthal, M., & Glenn, L. (2018, March 30). *Review of proprietary hawthorn extract WS® 1442 for treating heart failure*. HerbalGram. https://www.herbalgram.org/resources/herbclip/issues/2018/bin_589/031831-589/.
56. Opuni, K. F. M., Kretchy, J. P., Agyabeng, K., Boadu, J. A., Adanu, T., Ankamah, S., Appiah, A., Amoah, G. B., Baidoo, M., & Kretchy, I. A. (2023). Contamination of herbal medicinal products in low- and middle-income countries: A systematic review. *Heliyon*, *9*(9), e19370. https://doi.org/10.1016/j.heliyon.2023.e19370.
57. Ge, B., Zhang, Z., & Zuo, Z. (2014). Updates on the clinical evidenced herb–warfarin interactions. *Evidence-Based Complementary and Alternative Medicine*, *2014*, 957362. https://doi.org/10.1155/2014/957362