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HOLISTIC HEART HEALTH: A REVIEW OF TRADITIONAL CARDIOPROTECTIVE AGENTS

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ABSTRACT

The global rise of incidents related to cardiovascular disorders has increased considerably over the past few years claiming multiple lives. To add to these incidents, COVID-19 associated cardiovascular complications have worsened the outlook for numerous patients. Acute coronary syndrome and stroke were found to be the most common afflictions.

Conventional treatment regimes have succeeded in management of most cases of cardiovascular disease but possess limitations such as increased risk of side effects, post-surgical complications and therapeutic failure in some cases.

To obtain additional therapeutic benefit, drugs of natural origin that have been widely used as cardiotonics and cardioprotective agents can be introduced or supplemented with conventional medication and other treatment regimes.

These drugs inherently possess various pharmacological activities such as antioxidant, anti-hyperlipidemic, antihypertensive and other complementary effects as well as direct action on cardiac tissue by virtue of which they can be employed to prevent, mitigate and protect against cardiovascular disorders. Additionally suitable lifestyle modifications can also go a long way in improving the outcome of heart disease.

The following review highlights certain drugs of natural origin such as *T.Arjuna, Shilajit, W.somnifera, G. glabra, A.lebbeck, T. terrestris, T.cordifolia , E.officinalis* and *T.chebula*.that have been mentioned in texts of Ayurvedic, Unani and other forms of traditional medicinal literature.

Keywords: Cardiovascular disease, traditional medicine, phytoconstituents, cardioprotective, cardiac markers,anti-inflammatory, antioxidant

INTRODUCTION

The past few decades have witnessed a global surge in incidences related to cardiovascular disease which is the ultimate outcome of poor lifestyle management. Cardiovascular diseases or CVDs have resulted in over 17.9 million deaths worldwide in 2019 accounting to more than thirty percent of total deaths. Heart attack and stroke were found to be the highest contributors to these cases by being attributed to 85% of these deaths **[1]**.

The recent years have also witnessed the COVID-19 pandemic. According to the WHO, over 6 million deaths have been reported due to coronavirus infections **[2]**. These severe infections have not only caused irreparable damage to the respiratory health of patients but have also demonstrated severe cardiovascular complications through various mechanisms such as direct myocardial injury, increased oxidative stress and inflammation and coronary thrombosis to name a few and have also led to development of cardiovascular disorders **[3-4]**.

Conventional treatment options of cardiovascular diseases generally include the use of medications such as beta blockers, cardiotonics, anti-hypertensives, diuretics, anti-hyperlipidemic agents which are accompanied with a plethora of side effects thus creating a need for more effective and safe therapeutics for management of CVDS **[5-9]**.

Commonly observed side effects and limitations of conventional treatment regimes can be summarized as given:

Table 1: Summary of side effects associated with conventional cardiovascular therapeutics

Conventional therapeutics	Side effects
Surgical methods	Angioplasty- arrhythmia, bleeding at site of catheter introduction, damage to arteries, allergic reaction [7] Coronary Artery Bypass Graft - Atrial fibrillation, infections, reduced renal function, stroke, heart attack [8] Pacemaker implant - Blood clots, infections, pneumothorax, twiddler's syndrome [9]
Beta blockers	Rebound hypertension, worsening of MI and angina, dizziness [5-6]
ACE inhibitors	Hypotension, renal failure, hypokalemia, persistent cough, angioedema, fetopathy, headache [5-6]
Angiotensin receptor blockers	Hypotension, hyperkalemia, fetopathy [5-6]
Antiarrhythmic agents	Cardiotoxicity, Torsades de pointes, GI disturbances, neurological disturbances, hypotension, bradycardia [5-6]
Nitrates	Hypotension, palpitation, headache, dizziness [5-6]
Calcium channel blockers	Hypotension, bradycardia, precipitation of CHF, constipation, edema [5-6]

DRUGS OF NATURAL ORIGIN AS CARDIOPROTECTIVE AGENTS

For centuries, traditional systems of medicine have been used worldwide for treatment of various diseases. About 30,000-45,000 plant species native to the Indian subcontinent have demonstrated therapeutic potential and many of these indigenous plants as well as drugs of mineral and animal origin have been employed in traditional medicinal systems such as Ayurveda, Unani and Siddha in different formulations that can be used for a wide array of medicinal purposes **[10-11]**.

Drugs of natural origin used traditionally in the treatment of cardiovascular diseases contain a multitude of different phytoconstituents which act through various mechanisms of action as described.

Terminalia Arjuna

The bark of the evergreen *Terminalia Arjuna* belonging to the Combretaceae family has been used as a potent cardioprotective agent. Arjuna is native to India and Sri Lanka. It is known to contain a wide range of phytoconstituents such as polyphenols, flavonoids, tannins, triterpenoids, sterols and saponins **[12-14]**.

Table 2: Chemical Constituents of *T.Arjuna*

Class	Constituent
Triterpenoids	**Arjunolic acid Terminic acid, Arjunin, Arjunic acid, Terminoltin, Arjunoside III and IV, Arjunaphthanoloside [12-14]**
Glycoside	**Arjunolone,Arjunoltin, Arjunaphthanoloside Arjunetin, Terminoside A, Arjunic acid Arjungenin,Arjunglucoside I and II[12-14]**
Tannins	**pyrocatechols, punicallin, punicalagin, terchebulin, castalagin and casuarin Terflavin C Castalaigen [12-14]**
Flavonoids and Polyphenols	**Arjunolone, Quercetin,Luteolin, Baicalein, kaempferol Gallic acid, Ellagic acid [12-14]**

Figure 1: *T.Arjuna* plant [13]

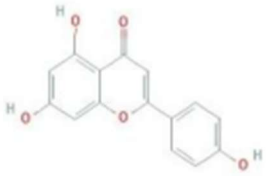

Figure 2: Structure of Arjunolic acid [13]

Mechanism of cardioprotective action: Glycosides present in Arjuna bark act as cardiac stimulants. Studies have demonstrated that alcoholic extracts of arjuna bark increased the auricular as well as ventricular contraction force in rabbit heart following intravenous administration. Furthermore, a rise in coronary flow was also noted. A positive

inotropic effect was observed post administration of aqueous extract in isolated frog heart. Dose dependent hypotension was seen for about 90 minutes following intravenous administration of aqueous extracts (40 mg/kg) of arjuna bark to anesthetized dogs.

Interestingly,a dose dependent negative inotropic and chronotropic effect was observed after administration of alcoholic extracts of arjuna on isolated murine atria. A notable extension of Arjuna bark's cardioprotective action also lies in its ability to regulate thyroid function **[15]**.

Arjuna bark extracts are rich in flavonoids which are the major cardioprotective agents as they correct endothelial dysfunction, bring about vasodilation thus reducing arterial pressure, reduce atherosclerotic plaque formation by decreasing the extent of platelet aggregation and by elimination of oxidized modified low density lipoprotein which is a major contributor towards atherosclerosis. Flavonoids and polyphenols present in arjuna bark act as antioxidants and demonstrate free radical scavenging activity. These compounds also act as inhibitors of prostaglandin synthesis and inhibitors of COX-1 and 2 enzymes thereby demonstrating anti-inflammatory activity. Aqueous and alcoholic extracts also thus contributing to its overall cardioprotective action as most cardiovascular diseases are linked to oxidative stress and inflammation **[15-16]**.

Studies conducted on Wistar rats that were fed high cholesterol diets and were later treated with Arjuna bark extracts revealed that Arjunic acid, arjun glycosides and tannins act as lipid lowering agents that effectively reduced total cholesterol and triglyceride levels and can enhance adiponectin. These extracts inhibit lipid peroxidation and the enzyme HMG CoA reductase which plays an essential role in cholesterol synthesis. An effect on free radical generation in THP-1 cells was also noted which is involved in inflammatory conditions characterized by the presence of markers such as TNF alpha, E-selectin and VCAM-1. This mechanism augments its cardioprotective action by lowering the risk of development of atherosclerosis, thus making it useful for prevention or mitigation of atherosclerosis **[16-17]**.

The bark of *Terminalia arjuna* can be incorporated alongside standard medical treatment for better management of cardiovascular disorders.

Shilajit

Shilajit (*Asphaltum*) is a drug of herbo-mineral origin that has gained a high ranking position in ancient texts throughout the world.

The use of this drug has been mentioned in the Sushruta samhita and Charaka Samhita as a *Rasayana* which is known to improve longevity and promote rejuvenation. Shilajit is obtained as a resin and is found in various mountainous regions of India, Pakistan, Afghanistan, Yemen, China, Nepal and other areas **[18]**.

Table 3: Chemical Constituents of Shilajit

Class	Constituent
Humic substances	Humic acid, Fulvic acid [19-20]
Organic acids	Benzoic acid, hippuric acid , oxalic acid, mumic acid, succinic acid, citric acid etc.[19-20]
Phytoconstituents	Carbohydrates,proteins,lipids, alkaloids,terpenoids,cardiac glycosides, tannins, saponins etc.[19-20]
Minerals	Iron, copper, zinc, magnesium,manganese, potassium, calcium etc. [19-20]

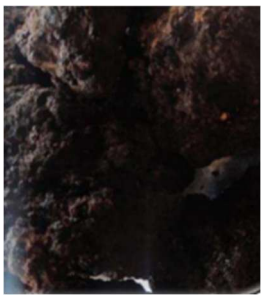

Figure 3: Raw Shilajit 21

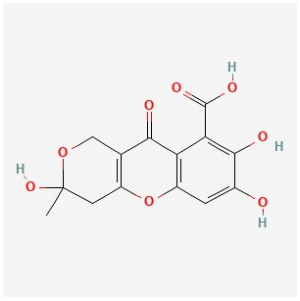

Figure 4: Structure of Fulvic acid

Mechanism of cardioprotective action: Shilajit acts as a powerful cardioprotective agent. According to Ayurvedic literature, Shilajit when used with *Arjun Kwath* is suitable for treatment of *hridayroga* or heart disease 21. Studies conducted on rats exposed to myocardial damage induced by isoproterenol (ISO) revealed the cardioprotective potential of Shilajit when given prior to high doses of isoproterenol. Shilajit decreased the negative effects of ISO on heart tissue by maintaining levels of maximum and minimum dp/dt (contraction velocity) and by lowering levels of cardiac troponin which are found to be elevated in conditions associated with cardiovascular damage **[21-23]**.

Shilajit also augments tissue oxygen levels by increasing the oxygen carrying capacity of blood thereby preventing a significant decline in oxygen levels during ischemia.

Owing to a powerful anti-inflammatory effect, Shilajit also decreases histamine release, prevents leukocyte infiltration in damaged myocardial tissue and protects against endothelial damage. Shilajit can also be used for attenuation of reperfusion injury following ischemia **[21-23]**.

Furthermore, Shilajit also demonstrates an antihyperlipidemic effect comparable to simvastatin. Maintenance of cholesterol levels

also plays a major role in management of cardiovascular disorders involving atherosclerotic plaque formation **[21-23]**.

Shilajit also improves the hematocrit value which is a marker used for diagnosis of anemia and cardiovascular disorders 24. Mineral content also greatly affects the overall cardiovascular properties of Shilajit. of the many varieties available, Tamra Shilajit predominantly contains copper which has shown potential as a pro angiogenic agent by increasing the overall branching of blood vessels in chick embryo through its control over factors such as hypoxia inducing factor α and also through its action on transforming growth factor (TGFβ) which plays a significant role in formation of new vessels **[25-26]**.

Various activities associated with Shilajit such as cardioprotective, anti-inflammatory, anti hyperlipidemic and antioxidant effects contribute to the potential of Shilajit in cardiovascular disease management.

Withania Somnifera

Withania Somnifera of the Solanaceae family, commonly known as Ashwagandha or Indian ginseng has been a widely used drug in various systems of traditional medicine especially in various regions of the Indian subcontinent, the middle east, and parts of Africa. Ashwagandha is extensively documented in the Charaka samhita, Sushruta samhita, Rasaratnasamukaya and other Ayurvedic texts in which it is considered as a Sattvic kapha Rasayana. It has also been mentioned in notable Unani texts such as Kitab al Hashaish. Though the roots of this shrub are most commonly used, other parts such as leaves, fruits and flowers have also been used as medicine **[27-29]**.

Table 4: Chemical Constituents of *Withania Somnifera*

Class	Constituents
Withanolides and related compounds	**Withanolides A-D, Withaferin A, Withanone,Withanosides[29-30]**
Alkaloidal compounds	**Anaferine,tropine, pseudotropine, withanine, pseudo withanine, withasomnine, ashwagandhin, mesoanaferin, visamine [29-30]**
Amino acids and organic acids	**Aspartic acid, proline, alanine, glycine, glutamic acid , tyrosine, cysteine, tryptophan, myristic acid, palmitic acid, linoleic acid [29-30]**
Miscellaneous compounds	**Reducing sugars, Hentriacontane, withaniol, iron etc[29-30]**

Figure 5: *W. somnifera* roots [27]

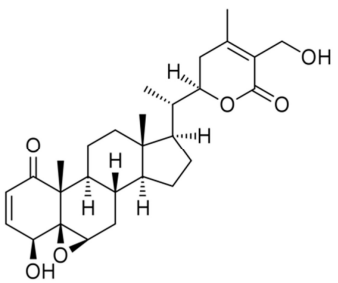

Figure 6: Structure of Withaferin A [27]

Mechanism of cardioprotective action: Ashwagandha acts as a cardioprotective as well as a cardiotropic agent by virtue of its antioxidant action and activation of nuclear factor erythroid 2 related transcription factor as well as by increasing the activity of phase II microsomal enzymes.

Various studies demonstrate the decrease in biochemical and histopathological parameters related to cardiotoxicity in various rat models including coronary artery occlusion model, doxorubicin induced toxicity model and isoproterenol induced toxicity model. The overall effect observed was a significant decline in levels of cardiac troponin, lipid peroxidase and other markers while also maintaining a healthy lipid profile **[30-31]**.

Aqueous extracts of Ashwagandha led to significant relaxation of precontracted aorta of murine model and also caused dose-dependent lowering of systolic and diastolic blood pressure by possibly reducing cardiac sensitivity towards adrenaline and similar adrenergic neurotransmitters. A vasodilatory effect is observed due to generation of NO as well as its adaptogenic effect on the sympathetic nervous system. Additionally lowering levels of oxidative stress aggressors such as bcl-2, P.carbonyl MPO and MDA as well as reducing concentration of calcium ions also contribute to prevention of cardiotoxicity. The effects observed against lowering of oxidative stress can also be extended to management of cardiovascular damage by COVID induced hyper-inflammation **[32-33]**. Ashwagandha demonstrates a variety of therapeutic actions thus warranting its use in cardiovascular well-being.

Glycyrrhiza glabra

Glycyrrhiza glabra (Leguminosae) is commonly known as liquorice and has been used frequently as a demulcent, expectorant and flavoring agent. The drug is found in many regions of the world and has found its place in different systems of natural medicine owing to excellent antioxidant and anti-inflammatory activity.It has recently gained fame for management of COVID associated inflammatory conditions **[34-35]**.

Table 5: Chemical Constituents of *Glycyrrhiza glabra*

Class	Constituent
Saponin glycoside	Glycyrrhizin [36-39]
Flavonoids	Liquiritin, isoliquiritin, liquiritigenin, rhamnoliquiritin, glyasperin A-D, chalcones, kumatakenin,glabrol,glabridinlicoricone [36-39]
Coumarins and phenols	arylcoumarins, isolicopyranocoumarin, hedysarum coumestan, umbelliferone, herniarin [36-39]
Polysaccharides	L-arabinose, L-rhamnose, D-galactose, D-galacturonic acid, D-glucose, galacto-glucan type polysaccharides [36-39]
Miscellaneous	Essential and volatile oils, quinoline and isoquinoline alkaloids, β sitosterol,amino acids,amines,gums [36-39]

Figure 7: G.glabra roots [34]

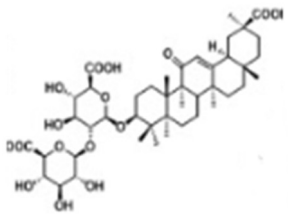

Figure 8: Structure of Glycyrrhizin [34]

Mechanism of cardioprotective action: Glycyrrhizin, the major active component of liquorice acts by reducing inflammation, lowering lipid levels, mitochondrial and oxidative damage due to ischemia in cardiac tissue during conditions of hyperglycemia. Levels of TGF β were found to be lower in groups of rats treated with glycyrrhizin. It also showed significant benefits in attenuating cardiotoxicity induced by doxorubicin and also maintains levels of AST, CK-MB and SOD and improves viability of H9c2 cardiomyocytes **[40-42]**.

Glycyrrhizin also offers protection in coronary microembolism induced myocardial dysfunction by lowering levels of inflammatory mediators such as HMGB-1, IL-6, IL-β, TNFα, and iNOS. It also inhibits apoptosis of cardiomyocytes and decreases the expression of Bax and cleaved caspase-3 **[43]**.

Cardiac reperfusion injury can also be managed using extracts of liquorice in rats subjected to left anterior descending coronary artery. An improvement in various parameters such as mean arterial pressure, heart rate, contractility has been observed. A delay in progression of cardiovascular disease has also been observed owing to the antioxidant potential of liquorice **[44-45]**.

Glabridin, a flavonoid obtained from liquorice possesses pleiotropic activity, inhibits LDL oxidation and NADPH thereby interfering with various stages of atherosclerosis **[46]**.

Thus, through a combination of various mechanisms,liquorice possesses the potential for offering cardioprotection.

Tribulus terrestris

The fruits of *Tribulus terrestris*, a common weed belonging to the Zygophyllaceae family have been popularly used mainly for their steroidal phytoconstituents. It has traditionally been used as a tonic, stomachic, aphrodisiac, antihypertensive agent, diuretic, and for management of stones and urinary infections **[47-49]**.

Table 6: Chemical Constituents of *Tribulus terrestris*

Class	Constituents
Steroidal Saponins	**Furostanol and spirostanol saponins Diosgenin, Dioscine, protodioscin, yamogenin, prototribestrin,neoprototribestrin, chlorogenin, tigogenin(tribulosin), neotigogenin,hecogenin, neohecogenin, gitogenin, sarsapogenin,etc. [47-49]**
Flavonoids	**Kaempferol, quercetin, rutin, chrysin, astragalin, isorhamnetin, etc. [47-49]**
Alkaloids	**Tribulusterine, harmane, norharmane [47-49]**
Lignan amides	**Tribulusamides A,B and C, terrestriamide, 7-methyl hydroindanone [47-49]**
Miscellaneous	**Oligosaccharides, fructans di-p-coumaroylquinic acid, cinnamic acid and quinic acid derivatives [47-49]**

Figure 9: T.terrestris plant [47]

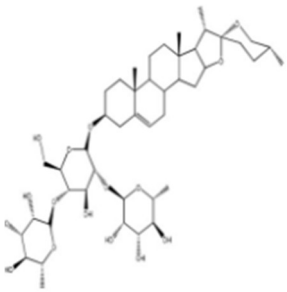

Figure 10: Structure of Dioscin [47]

Mechanism of cardioprotective action: Extracts of *T. terrestris* have been widely used for their cardioprotective benefits in management of conditions such as myocardial infarction, atherosclerosis, cardiac ischemia and reperfusion injury **[50-51]**.

A steroidal compound, tribulosin acts as a cardioprotective agent in situations of reperfusion injury following a bout of ischemia via Protein Kinase C (PKCε) It also leads to a reduction in levels of malondialdehyde, aspartate transaminases, creatine kinase and lactate dehydrogenase all of which are present during conditions of myocardial stress/injury **[50-51]**.

Flavonoids such as tribuloside, rutin and others play a significant role in reducing inflammation and oxidative stress. They also act as major ligands that interact with receptors involved in regulation of heart rate and mean arterial pressure such as ADRA1b as well as other receptors such as vasopressin, oxytocin, cholinergic and adrenergic receptors **[50-52]**.

The rate of myocardial apoptosis was also lowered due to inhibition of pro-apoptotic Bax and Caspase-3. Size of infarcts also decreases with tribulosin pre-treatment. An experiment conducted on rats exposed to anabolic steroids like stanozolol also demonstrates lowering of pro-apoptotic factors thus offering protection against steroid induced myocardial damage **[53]**.

Albizia Lebbeck

Albizia lebbeck, a deciduous tree belonging to the Fabaceae family, is found in several regions of the world including Asia, Australia, Africa, South America, Central America and the Caribbean.

It has found its place in various systems of alternative medicine in these regions and has been employed for the treatment of skin diseases, ulcers, respiratory diseases, night blindness and snake bites to name a few.

Table 7: Chemical Constituents of *A.lebbeck*

Class	Constituents
Flavonoids	Luteolin, geraldone, isookanin, lebbeckisoetin, chiakine[54-56]
Saponins and sterols	Albiziasaponins (A-E), Lebbeckosides (A-C), Lebbeckalysin, Complex triterpenoid saponins, spinasterols [54-56]
Tannins	D-catechin, D-leucocyanidin [54-56]
Essential oils	2-pentyl furan, (E) geranyl acetone, (E) α ionone [54-56]
Fatty acids	Oleic acid, linoleic acid, palmitic acid, stearic acid [54-56]
Hydrocarbons	tetradecane, hexadecane,octadecane, nonadecane, eicosane[54-56]
Miscellaneous	Protein,phytol , vitamin E , eugenol, D-mannitol, keto acids,glutamic acid, aspartic acid [54-56]

Figure 11: *A.lebbeck* plant [57]

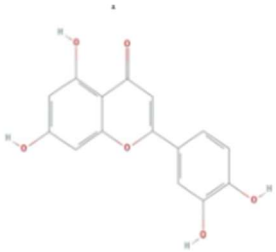

Figure 12: Structure of luteolin [57]

Mechanism of cardioprotective action:

The leaves of A.lebbeck contain cardiac glycosides and root extracts have been used as cardiac stimulants. Cardioprotective action can be mainly attributed to antioxidant activity which essentially targets ROS and reduces/prevents oxidative stress which generally leads to myocardial damage. Additionally anti-thrombotic effect has also been observed which further necessitates the need for the drug to be developed as a cardioprotective agent **[57-59]**.

Tinospora cordifolia

A perennial herbal plant, *Tinospora cordifolia* commonly known as Giloy is a member of the Menispermaceae family. It is indigenous to south east asian countries such as India, Sri Lanka and Bangladesh and is an important drug in various systems of Indian traditional medicine **[60-62]**.

Table 8: Chemical Constituents of *Tinospora cordifolia*

Class	Constituents
Alkaloids	Berberine, tinosporine, magnoflorine, n-formyl annonaine, palmatine, reticuline, jatorrhizine, menisperine [60-62]
Glycosides	Cordifolioside, syringin [60-62]
Terpenoids	Tinocordiside, tinosponone, 11-hydroxy muskatone, tinocordifilin, tinocordifoliside[60-62]
Carbohydrates and proteins	Arabinogalactan,α D-glucan ,guduchi immunomodulatory protein, glucose, arabinose, xylose, rhamnose, galactose, mannose[60-62]
Miscellaneous	Lignans, giloin, tinosporan acetate, octasanol, sinapic acid [60-62]

Figure 13: *T.cordifolia* plant [60]

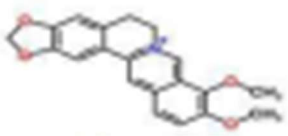

Figure 14: Structure of berberine[60]

Mechanism of cardioprotective action:

Root, stem and leaf extracts of *T.cordifolia* have been widely recognised for possessing cardioprotective properties. Studies have revealed its benefits in treating myocardial damage such as damage caused by physical occlusion of the coronary artery or cardiotoxins such as cadmium and cisplatin. It was demonstrated that following cisplatin treatment, cardiac damage (as seen during prolonged chemotherapy) characterized by disarrayed cardiomyocytes, interstitial edema and necrosis was observed in rats. These changes were ameliorated with *T.cordifolia* treatment

Cisplatin also increases oxidative stress and cardiac troponin levels which can be neutralized and managed by co-administration of *T.cordifolia* **[61-64]**.

Treatment of ischemia following coronary artery occlusion was also carried out using *T.cordifolia* during which a decrease in the size of infarcts,reduction in lipid peroxidase levels and prevention of reperfusion injury was observed. Treatment of MI using T.cordifloia in combination with atenolol and propranolol demonstrated a better outcome as compared to the beta blockers used alone **[61-65]**.

Alcoholic extract administration after calcium chloride induced arrhythmia led to lowering of intracellular sodium and calcium levels and dose-dependent increase in potassium levels was observed thus strongly suggesting anti-arrhythmic activity and indicating its potential as an all-round cardioprotective agent **[61-65]**.

Emblica officinalis

Emblica officinalis commonly known as Amla belongs to the Euphorbiaceae family. Its fruits are rich in vitamin C and have been popularly consumed as medicinal agents and also as nutritional supplements **[66-68]**.

Table 9: Chemical Constituents of *Emblica officinalis*

Class	Constituents
Phenolic acids and acidic compounds	Ascorbic acid,Gallic acid, ellagic acid4-hydroxybenzoic acid, coumaric acid, vanillic acid, syringic acid, vanillic acid, caffeic acid, chlorogenic acid [66-69]
Flavonoids	Derivatives of kaempferol,eriodictyol and quercetin, rutin,luteolin, apigenin, myricetin, naringenin, gallocatechin, epigallocatechin [66-69]
Tannins	Tannic acid, emblicanin A and B, phyllaemblicin B, punigluconoin, corilagin, geraniin, chebulagic acid Ellagitannins such as chebulinic acid, chebulagic acid, corilagin, angeraniin, isocorilagin, pedunculagin, phyllanemblinins A–F, and punigluconin,mucic acid gallate, monogalloyl glucose, mucic acid lactone gallate, digalloyl glucose [66-69]
Alkaloids	Phyllantine, phyllantidine [66-69]
Fatty acids	Stearic, linolenic, palmitic, oleic, linoleic and myristic acids [66-69]
Miscellaneous	Fibers, amino acids, minerals [66-69]

Figure 15: *E.officinalis* fruit [60]

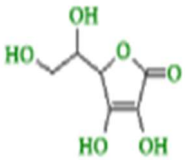

Figure 16: Structure of Ascorbic acid [60]

Mechanism of cardioprotective action:

E. officinalis shows excellent antioxidant and radical scavenging activity along with management of triglyceride and cholesterol levels mainly by inhibition of HMG-CoA reductase **[69-72]**.

A reduction in endothelial cell damage and anti-thrombotic activity has also been noted Pretreatment using Amla demonstrated restoration of cardiac and hemodynamic parameters in LAD occlusion in rats and also after isoproterenol induced myocardial damage **[70]**.

Furthermore, a decrease in systemic blood pressure on co-administration with regular antihypertensive agents was noted. A reduction in mean arterial pressure, and heart rate has also been observed along with reduction in cardiac hypertrophy and atherosclerosis **[69-72]**.

Terminalia chebula

Terminalia chebula (Combretaceae) commonly referred to as myrobalan/haritaki is commonly used in traditional medicine systems to revitalize the body and treat a variety of ailments such as disorders of the digestive system, infections and others. It forms a major component of triphala. It is a potent antioxidant and anti inflammatory agent and also provides therapeutic benefit in atherosclerosis, epilepsy, glucose metabolism etc. **[73-75]**.

Table 10: Chemical Constituents of *Terminalia chebula*

Class	Constituents
Tannins and phenolic compounds	Gallic acid, chebulinic acid, chebulic acid, terchebulin,punicagalin, terflavin, catechin, chlorogenic acid, ellagic acid, corilagin, tannic acid [73-75]
Flavonoids	Quercetin, kaempferol, rutin [73-75]
Sterols and lipoidal compounds	Sitosterol, daucosterol, palmitic acid, furfural [73-75]
Miscellaneous	Ascorbic acid, quinic acid, shikimic acid, glucose, fructose, vitamin E, amino acids [73-75]

Figure 17: *Terminalia chebula* plant [75]

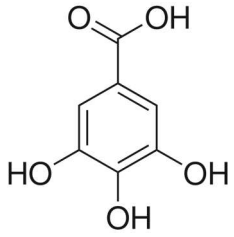

Figure 18: Structure of gallic acid [75]

Mechanism of cardioprotective action: *T. chebula* mainly acts by management of lipid metabolism by decreasing levels of cholesterol in the liver and heart through its inhibitory action on cholesterol synthesis and by increased excretion of cholesterol. Studies conducted on wistar rats have revealed a decreased atherogenic index following treatment with methanolic extracts of *T chebula*. Decrease in aortic plaque formation was also seen along with improvement in myocardial and enzyme markers.

Cardiotonic effect with increase in cardiac output without significant alteration of heart rate was observed in hyperdynamic and normal frog hearts **[73-74]**.

Investigations on male and female wistar rats have also demonstrated protective action of *T.chebula* extracts against doxorubicin induced myocardial damage by lowering serum levels of cardiac troponin, lipid peroxidase, cardiac GSH and SOD while increasing cardiac CK-MB activity and catalase through its potent antioxidant effects. Recovery of cardiomyocytes was better and structural distortions were reduced when animals were given pre-treatment with *T.chebula* **[76-77]**.

CONCLUSION

The significance and relevance of traditional medicinal agents through centuries has remained unparalleled. Modern scientific studies have also extensively documented and confirmed the therapeutic benefits of these agents. Phytoconstituents and other drugs of natural origin have served as the backbone of synthetic medicine; acting as scaffolds to structurally modify synthetic and semi synthetic moieties to improve their therapeutic efficacy. Natural remedies and

treatments can be incorporated into modern formulations or used alongside conventional treatment regimes to improve various aspects such as bioavailability, therapeutic efficacy, safety and mitigation of side effects.

The demand for an increase in alternative medicine to improve the outcomes of lifestyle related disorders especially those of the cardiovascular system can be met by introducing formulations of plant extracts possessing cardioprotective properties into daily routines along with necessary lifestyle modifications to ensure overall well-being.

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