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Review Article

Evidenced-based Phytotherapy Overview: Protective Role of Diverse Bioactive Phytochemicals in Myocardial ischemia through Pharmacodynamics and Molecular Mechanisms

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Abstract

During the last decades, the rise in the number of patients with Cardiovascular Disease (CVDs), a class of chronic disease including Myocardial Iinfarction (MI) has threatened the healthcare system all over the world largely due to increased mortality. Thus, emphasizing the urgent need for an efficient drug without any deleterious adverse side effects.

Presently used synthetic drugs clinically in the treatment of CVDs, especially MI do provide a good chance of survival but are associated with adverse side effects and are costly. Hence, the demand to search for safer, effective, and natural products from plants is increasing. Plants are rich in biochemicals, which are secondary metabolites (comprised of polyphenols, saponins, flavonoids, alkaloids, and many more) also called phytochemicals, possessing antioxidant, anti-inflammatory, antilipidemic, and many other diverse biological activities that may be useful for the prevention and/or treatment of MI. However, many bioactive extracts lack much-needed pre-clinical pharmacological, toxicological, as well as phytochemical data. Some of these phytochemicals may be useful and play a prominent role in cardioprotective activity either prophylactically or as a complementary medicine or adjuvant along with currently used clinical drugs. The present review addresses the role of different bioactive herbal extracts and several types of phytochemicals in the protection of MI along with their effects on hemodynamics, biochemical markers, and molecular mechanism(s) of action. It also presents future perspectives and novel approaches for the development of evidence-based new-generation cardioprotective medicines of plant origin.

Introduction

Cardiovascular Diseases (CVDs) include ischemic heart diseases, atherosclerosis, coronary artery diseases, arrhythmias, congestive heart failure, cardiomyopathy, peripheral arterial and rheumatic heart diseases, and among CVDs, myocardial Infarction (MI) a major cause of mortality, morbidity all over the world. Around 1.4 million deaths are due to myocardial infarction out of 17.5 million cardiovascular disease-related deaths. It has been predicted that 23.6 million people will be suffering from CVDs annually by 2030. The modifiable risk factors for CDs are: lifestyle and inbuilt behaviour of the individual, including smoking, obesity, stress, diet, lack of physical activities, and diseases like hypertension, dyslipidaemias, diabetes mellitus, hypercholesteremia [1]. Myocardial infarction can be medically defined as necrosis of the cardiac muscles due to continuous acute myocardial ischemia: these are, spontaneous (MI type 1), MI secondary to an ischemic imbalance (MI type 2), cardiac death due to (MI type 3) and MI associated with revascularization procedure (MI type 4 and 5). Physiopathological changes/ abnormalities in blood pressure, heart rate, ECG, and cardiac tissue damage accompanied necrosis and apoptosis with significant alterations in morphological, physiological, and cardiovascular functions. Generally, MI causes ventricular remodeling as a body-adaptive response largely because the ventricular function

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is meticulously regulated by mechanical and neurohumoral impulses. Ventricular remodeling occurs with the increased infarct area (size), followed by ventricular rupture and aneurysm development, as response to the local inflammatory process and then migration of cells (macrophages, monocytes, neutrophils) to the infarcted site. Late phases of remodeling, dilation of the ventricle and its shape and structural alterations lead to the stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, resulting in the release of natriuretic peptides and participate in the development of mural hypertrophy.

In addition to the aforementioned changes (physiological, morphological and pharmacological), other complex cellular, biochemical and pathological alterations occur which give greater insights to understanding the myocardial ischemic process in cardiac tissue and are explained below. a) Ischemia and energy failure: Loss of oxygen impairs mitochondrial phosphorylation, decreasing ATP, and increased anaerobic glycolysis causes intracellular acidosis due to lactic acid accumulation. b) Ion pump dysfunction: Decreased ATP formation disrupts Na+/K+ ATPase pumps and calcium ATPase, leading to hyperkalemia from cellular potassium efflux. Also increased intracellular Na^+ and Ca^+ levels causes arrhythmias and decreased contractile function cellular swelling and Ca+ overload triggering apoptosis and necrosis excessive calcium and ROS cause mitochondrial membrane permeabilization and release of pre-apoptotic factors like Cytochrome C c) Mitochondrial damage: Increase of creative stress due to membrane lipid peroxidation product like malonyl aldehyde (MDA), lead to the formation of reactive oxygen species (ROS) d)Oxidative stress: Increased ROS damages lipid membrane integrity, protein and DNA structure. Further, the elevation of free radicals, superoxide anions, hydroxyl ions, and H_2O_2 ions results in depletion of tissue-bound antioxidant enzymes and reduces DNA synthesis [2] (Figure 1).

In addition, oxidative stress elevates neutrophil count, which in turn causes a release of leukotrienes and, the release of lysosomal enzymes from the sac (due to increased free radicals causing loss of membrane permeability). Cardiac cell membrane damage allows leakage of intracellular protein, the most sensitive and specific (and some non-specific) biomarker, such as troponin I and T and myoglobin and Lactic Dehydrogenase (LDH), matrix metalloprotein-1 (MMP-1), creatinine kinase isoenzyme MB(CK-MB) and heart-type fatty acid binding protein ($FABP_3$) [6].

Inflammatory mediators: The cellular ROS promotes the production and release of pro-inflammatory biomarkers such as Tissue Necrosis Factor-α (TNF-α), Interleukin (IL-6), and Interleukin (il1-β) which amplifies local and systemic inflammation. In the context of oxidative stress JNK, NF-Kb, (cJun N-terminal kinase), NF-kB (Nuclear factor kB), and NLRP3 (Nucleotide binding domain leukin-rich repeat containing protein3) are key signaling molecules the primary function to trigger inflammatory response by activating various genes when cell experience excessive (ROS), often leading to cascade of cellular events aimed at mitigating the damage and but can also contribute cardiac tissue damage if dysregulated; JNK act as a kinase that activates inflammatory pathways NFkB

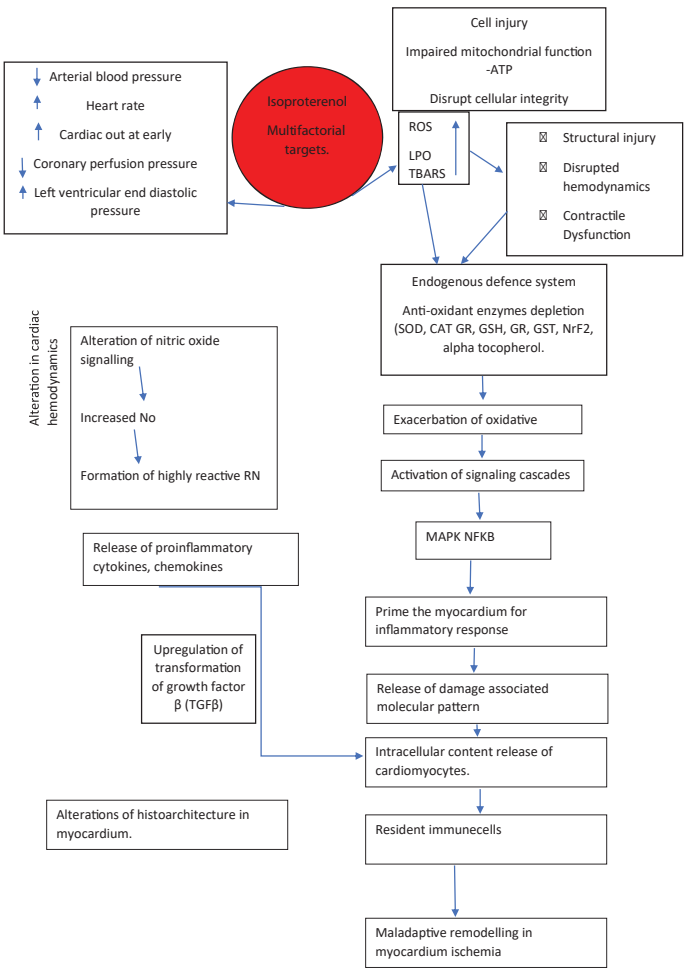

Figure 1: Pathophysiological alterations of Myocardial infarction induced by Isoproterenol-β receptor affecting multifactorial targets [3–5].

is a central transcription factor regulating pro-inflammatory genes, and NLRP3 is a key component of the inflammasome complex, which amplifies inflammatory responses.

Histopathological/histoarchitectural studies of cardiac tissue following MI also help to understand the integrity of the myocardial cell membrane, necrosis, muscle fibers with inflammatory cells, muscle fragmentation, edema, and many other muscle architectural changes. Understanding these physiological, cellular, biochemical, and physiological alterations in MI is crucial for diagnosis and management and for developing therapeutic strategies to minimize myocardial damage and improve patient outcomes. Highly Sensitive C-Reactive Protein (HSCRP) is also a marker of systemic inflammation, and vascular damage, like endothelial cell dysfunction, which leads to increased vascular permeability and platelet adhesion.

Many chemical cardiotoxic agents such as Isoproterenol (ISO) (a synthetic beta-adrenergic agonist), chemotherapeutic drugs, mainly anti-cancer drugs doxorubicin alone or with transtuzumas nandrolone, cisplatin, bleomycin cyclophosphamide, paclitaxel, methotrexate, carbon tetrachloride and placing ameroid constrictor, ligation of the left anterior descending coronary artery are used in producing experimental myocardial ischemia in rodents. Genetically

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induced knockout mice are also used, which provides greater insights into the structural and functional role of specific proteins that are associated with the myocardial injury and potential therapeutic interventions. However, the isoproterenol (ISO) model is widely used as the middle toxicant because the myocardial damage is similar to that observed in acute MI in humans [6–8]. ISO model may help to understand the pathologies in signal transduction, energetics, excitability, and contractility that are involved simultaneously to induce quality dysfunction and heart failure. This model is found to be useful for studying the structure and functional adaptation of myocardium during the progress of cardiac apoptosis response towards maladaptive hypertrophy and insufficiency.

In this review, we are addressing and discussing the effects of natural products covering plant-derived herbal formulations (based on the old traditional system of medicine in different countries), plant extracts, and phytochemicals on ISO-induced MI rodent model and a few instances of anti-cancer drug-induced MI. We also report key mechanisms of these natural products' therapeutic effects, emphasizing the role of biomarkers, oxidative stress, inflammatory process, cardiac contractile function, endothelial vascular dysfunction, and the importance of modulation of molecular pathways such as Nrf2, NF-kB, p21 activated kinase (PAK1). In addition, the key challenges and prospectus of natural products intervention in kinetic vascular diseases present new insights in the development of potential treatments for myocardial ischemia/R injury (Figure 1) Experimental models developed to study MI and intricate physiological, biochemical and pathological alterations and also use for the initial evaluation of potential cardioprotective compounds.

Natural products/phytochemicals/herbal formulations, is a promising alternative approach for complementary medicine

Folk medicine practices are the oldest form of complementary alternative medicines in the Indian herbal system and the traditional Chinese medicine system dating back to 2000 years. Similarly, other countries' traditional medicinal system is also reported to be a useful source for exploring new medicines for the treatment of human disorders. As per the WHO report, there is an increasing demand for herbal medicines across the world, most specifically among Indian and Chinese communities.

As compared to conventional drugs, plant-derived drugs/medicines are better tolerated by the patients, have fewer side effects, and also better accessibility (availability). Phytochemicals indicated therapeutic benefits in the treatment of cardiovascular disorders and in preventing heart failure. Clinical trials, analysis of epidemiological studies, and pre-clinical research explain that the bioactive compound through dietary and therapeutic intervention is effective in preventing and treating cardiovascular diseases [3].

Phytochemicals contain polyphenols (a large group of bioactive compounds) which include flavonoids (comprises flavonoids, flavones, flavan-3-ols, anthocyanins, flavonoids and isoflavones and non-flavonoids are phenolic acids, stilbens, coumarins, vanilloids, alkaloids, diterpenes, sesquiterpenes, carotenoids, tannins and lignins. Polyphenols are known to exact beneficial effects in cardiovascular disease including myocardial infarction due to antioxidant, anti-inflammatory, anti-cardiac hypertrophy, anti-atherosclerosis, and anti-apoptotic activities via diverse and multiple molecular targets and act on different protective pathways (Figure 2). The various vital biological and molecular interactions with tissues and organs of this natural plant chemical have significant potential in the treatment of CVDs and hopefully will offer an effective therapeutic value in future applications [9].

Saponins and tannin stabilise cardiac membrane through by preventing calcium load and lipid peroxidation. Products of lipid peroxidation such as MDA and TBARS have been correlated with the structural injury of cardiac muscle cells disturb hemodynamics, and cardiac contractile dysfunction and integrity of cardiac function.

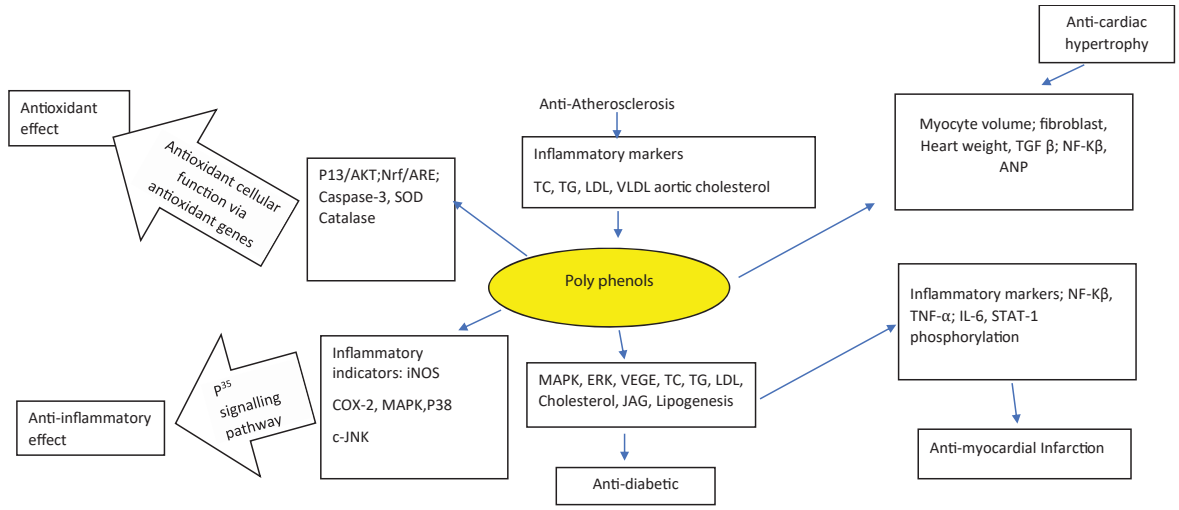

Figure 2: The figure depicts polyphenols play a protective role in MI mainly by combating oxidative stress, reducing inflammation, improving endothelial functioning, and regulating lipid levels, leading to protection from heart muscle damage during blood flow restriction to coronary arteries, essentially acting as antioxidants, anti-inflammatory to protect against cell death due to MI/injury [9,10].

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Plant extract normally contains several active secondary metabolite(s) hence it may produce different types of overlapping pharmacological actions (hypotensive, anti-platelet, antioxidant, anti-inflammatory etc.) which may be useful for assessing and predicting cardiac protective action. Many aqueous extracts of (*Punica granatus L., Allium sativum, Panax ginseng, Oxalis corniculata)* alcoholic extracts (*Withania somnifera, Labisia pumila var alata, Andrographis paniculata, Calotropis procera)* have exhibited scavenging of free radical and ROS, thereby decreasing lipid peroxidation and consequently reducing oxidative stress as well as myocardial cellular damage. Plant extract antioxidant activity is attributed to secondary metabolites because they are obtained directly from the plant without much processing/purification and concentration of active constituents such as flavonoid, glycosides or others [2,11–14]. The extracts of below-mentioned plants administration shown (*Elettaria cardamomum maton, Eugenia jambolana, Ganoderma lucidum, Saliva miltiorrhiza, Olea europea, Amaranthus viridis L., Terminalia arjuna, Zingiber officinale and Inula racemosa*) significant protection against ISO induced cardiac ischemia mainly by reducing oxidative stress which subsequently protects and maintain the natural permeability and structural integrity of cardiomyocytes from the oxidative damage preventing cardiac serum biomarkers enzymes SOD, CAT, Gpx, GSH, GR, GST, troponins (cTnT), ALP, SGDT, GGT, CK-MB, LDH improves mitochondrial function and ATP production.

Some of the plant extracts such as *Withania somnifera, Picrorrhiza kurroa, Desmodium gangeticum L.*, have shown hypercholesterolemia and hypoglycemic activity through inhibiting effect on cholesterol esterase, which hydrolyzes dietary cholesterol esters, leading to optimum levels of serum cholesterol and esterification of HDL cholesterol by LCAT. *Urtica parviflora Roxb* extract decreases cholesterol biosynthesis, enhanced bile acid secretion, and stimulates the LDL-C receptor mediated catabolism.

1. *Curcumin*

It is a natural lipophilic polyphenol highly pleotropic molecule, widely used in Ayurveda and Chinese medicine. It is isolated from the roots of *Curcuma longa*, a polyphenol more particularly a diaryl heptanoid (group of curcuminoids), and exerts anti-inflammatory, antioxidant, neuroprotective, hepatoprotective, and cardio-protective activities, and is known as the wonder drug of life [15–18]. It improves heart function and ameliorates cardiac tissue damage due to reduction of oxidative stress and cellular apoptosis by activation of phosphorylation of JAK 2 and STAT 3, increasing BCl-2/Bax expression and inhibitory caspase-3. Curcumin has been experimentally demonstrated in rodents to produce anti-atherosclerotic activity mainly through its protection against inflammation and antioxidant activity, modulation of cholesterol homeostasis and inhibition of platelet aggregation [19]. Also, the atherogenic index was reduced, and the histoarchitecture of the aorta was improved [20].

The anti-inflammatory effect of curcumin is largely mediated through inhibition of inflammatory mediators such as cyclooxygenase-2, lipoxygenase, enzymes involved in lipid mediators generation, which are implicated in inducing inflammation via arachidonic acid metabolism, and inducible nitric oxide synthase (iNOS) [21]. Abnormal proliferation of vascular smooth muscle cells (VSMC) and mononuclear cells are also shown to participate in the progression of CVDS including atherosclerosis. The vascular antiproliferative effect of curcumin has also been established by employing the LDL knockout mice model. In this model. Curcumin causes heme oxygenase-1 (HO-1) activation, an enzyme known to play a regulatory role in the reduction of growth of vascular smooth muscle cells. Further, it has been shown that induction of HO-1 causes a reduction in atherosclerotic lesions in LDL receptor knockout mice. Curcumin is known to induce HO-1 via activation of Nrf2 - dependent in a variety of cells of the cardiovascular system (example vascular endothelial cells, vascular smooth muscle cells, and human aortic smooth muscle cells). Hence, the Curcumin anti-proliferative effect is mainly related to its ability to induce HO-1 [23,24]. Curcumin encapsulated Poly (lactic-co-glycolic) acid nanoparticles have also been developed to improve delivery and better absorption.

2. *Salvianolic acid* A

It is (isolated from *Saliva miltirrhiza* Bung) in studies in natural product chemistry due to its antioxidant, anti-fibrotic, anti-inflammatory, anti-platelet aggregation, and inhibition of JNK/p13K/AKT signalling pathways shown protection in I/R injury and improve heart function and prevented cell apoptosis following I/R damage. It has been further demonstrated that *Salvianolic acid* regulates intracellular signaling pathways in vascular endothelial cells, smooth muscle cells, as well as cardiomyocytes both in *in-vivo* and *in-vitro* using cardiovascular stimulus. It is observed that the cardiovascular protection of *Salvianolic acid* is due to scavenging oxygen species, reduction of leucocytes, and endothelial adhesion molecules expression on vascular endothelial cells via regulating intracellular kinase activity. This pathway inhibition the kinase-associated signaling pathway and also participates in the anti-inflammatory activity.

In addition, competitive binding of *Salvianolic acid* to the target proteins to interrupt protein-protein interactions leads to cardiovascular protection [25].

3. *Astilbin*

It is a flavonoid, isolated from the roots of *Smilax china* L. used in Chinese medicine clinical practice. *Astilbin* improves heart function recovery caused by myocardial infarction damage via inhibiting inflammatory reactions and reducing HMGB1, phosphorylating NF-kB in ischemic myocardial tissue [26].

4. *Eupatilin*

A flavonoid isolated from the *artemisia* plant, shown to exert antioxidant, and anti-inflammatory activities. Further, it elevates myocardial I/R damage through reducing ROS and cell apoptosis by activating the AKT/glycogen synthase kinase-3β

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(GSK-3β) signaling pathways. It is reported to be beneficial in the treatment of myocardial I/R [27].

5. *Ocimum sanctum Linn* (OS)

Kavita et al (2015) have reported that methanolic extract of OS contains (cirsilineol, circimaritin, isothymusin, apigenin, and rosameric acid) and its pretreatment decreased inflammation in cardiac myocytes of isoproterenol-induced myocardial infarction in rats. The protective effect has been attributed to down regulation of oxidative stress and arachidonic acid pathway. The alcoholic extract of *Curcumin*, *Ginkgo biloba* and *Ocimum sanctum* treatment individually and in the combination for 60 days on isoproterenol-induced necrosis in rats showed a significant decrease in the elevated serum lysosomal enzymes (aspartate aminotransferase, lactic dehydrogenase and creatine phosphokinase) and the elevated MDA formation and restored the depleted antioxidant enzyme (GSH, Gpx, GR, SOD, CAT). Furthermore, improved heart hemodynamics and alterations of the histoarchitecture of the heart. A greater degree of protective effect was observed in the combination treatment group and a better effect on all these sensitive biomarkers and other evaluation paradigms. The cardioprotective activity of the above-mentioned plant extract has been attributed to the amelioration of oxidative stress and membrane stabilizing effect via flavonoids, phenolic compounds, and hydroxy methoxy and 1-3-di ketone conjugated form of curcumin, and known to be a potent antioxidant [16,17,27–29].

6. *Ginkgo biloba*

Belongs to the family Ginkgoaceae, is a Chinese herb and is the only surviving member of the Ginko old living tree species on the earth. Chemically, the active constituents of *Ginkgo biloba* leaf flavone glycosides (Kaemphferol, quercetin and isohamnetin) diterpene lactones- Ginkgolides A, B,C M, J and bilobide and the biflavones ginkgetin, bilobetin. *Ginko biloba* phytosomes (GBP-Ginkoselect manufactured by Indena Italy), pre-treatment for 21 days produced significant cardioprotective activity on isoproterenol-induced cardiac ischemia in rats. The elevated various serum lysosomal cardiac markers enzymes such as AST, LDH and CPK the depletion of antioxidant enzymes GSH, SOD, CAT, Gpx and GR and increased level of MDA are prevented and reversed respectively with the treatment of *Ginkgo biloba* phytosomes. The cardioprotective effect of *Ginkgo biloba* phytosome may be due to an augmentation credibility effect of Ginkgo biloba may be due to the augmentation of endogenous antioxidants and the inhibitory effect on lipid peroxidation of myocytes membrane via stabilization of the ROS by reacting with them and getting oxidized to more stable less reactive radicals. Presumably, the high reactivity of OH group of flavonoids is responsible for this free radical scavenging activity [30,31].

7. *Honokiol*

A natural bioactive polyphenol compound isolated from the bark, leaves, and seed cones of the plant *Magnolia officinalis,* a traditional Chinese medicine used for vascular diseases. Honokiol has shown anti-inflammatory, antioxidant, neuroprotective, and cardioprotective activities in rodent models. Honokiol extract treatment reduced myocardial infarction injury and it promoted autophagic flux in C57BL/ mice. The extract also reduces levels of inflammatory cytokines (e.g. TNF-α, IL-6) and inhibits NF-kB activation [32].

8. *Orientin*

It is a flavonoid of *Persicaria orientalis Spach*, a traditional Chinese herb (that contains flavonoids, phenolics, saponins, etc). The flavonoids are classified as C-glycoside of the luteolin (chemically known luteolin8-c-glucoside) its pharmacological activities reported are antioxidants (scavenging free radical ROS and protecting cells and tissues from oxidative stress) anti-inflammatory effects (suppress the production of pro-inflammatory cytokines and mediators such as TNF-α, IL-6 and inhibition of inflammatory signal pathway NFkB, MAPK, cardioprotective and improving cardiac function largely through mitigating oxidative damage and neuroprotective (reducing oxidative stress and inflammation in neuronal cells) [33].

9. *Icariin*

It is an active component from Epimedium and its metabolites, a natural flavonoid glucoside, and shown to protect myocardial I/R damage in rats, reduce IS, increase I/R injury, antiproliferative and inhibits remodelling. Decrease cardiac serum biomarkers CK, IMA, LDH and upregulate PI3K/ AKT/eNOS pathways in congestive heart failure rat model. *Icariin* promoted left ventricular function in ischemic issues. Hence, it may be useful in resisting I/R injury in the early stage [34].

Icariin nanoemulsion, a sustained release formulation, has shown improved cardioprotective action against doxorubicin-induced cardiotoxicity by improving antioxidant, anti-inflammatory and anti-apoptotic activity via targeting caspase-3/NF-kB/TNF-α, ILs pathways [35].

10. *Puerarin*

The chemical name for *Puerarin*, a major isoflavonoid (7-hydroxy-3-(4-hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-4H-1-benzopyran-4-one), a flavonoid extracted from the dried root of leguminous plant *Pueraria lobata*. *Puerarin* has many pharmacological activities such as cardiovascular protection, improve circulation, reduce myocardial oxy-consumption, prevent atherosclerosis effective in coronary heart disease, angina and myocardial infarction, anti-inflammatory (reduce inflammation and levels of inflammatory factors like IL-1β. Il-18 and TNF-α), antioxidant (increase in antioxidant enzyme activities scavenges ROS), neuroprotection, promote bone formation, reduce osteoclast formation, diabetic and hepatoprotective and many more [36,37].

11. *Resveratrol*

It is a stilbenoid polyphenol that has been demonstrated to have antioxidant, anti-inflammatory and anti-angiogenic

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effects. *Resveratrol* effectively eliminates free radicals due to its marked scavenging effects and also regulates antioxidant enzymes, showing anti-inflammatory effect, decrease production of various cytokines, and downregulates the activation of leukocytes and regulatory activation of leukocyte adhesion molecules or COX isoforms. It improves the survival of cardiomyocytes and inhibits ROS-mediated maladaptive hypertrophy, apoptosis, and fibrosis. More human clinical trials are required to confirm these effects [38].

12. *Baicalin*

A flavonoid that is isolated from the *Scutellaria baicalensis* georgi that conspicuously exerts anti-inflammatory, antioxidant activity. Improves chronic inflammation, immune imbalance, disturbances in lipid metabolism, apoptosis and oxidative stress. Thereby, it offers beneficial rules against the initiation and progression of cardiovascular diseases [39]. *Baicalin* is a promising therapeutic agent both prophylactic and therapeutically against the initiation and progression of CVDS such as atherosclerosis, hypertension, myocardial infarction and reperfusion, and heart failure. *Baicalin* alleviates the progression of atherosclerosis due to its hypolipidemic activity and inhibition of foam cell formation, reduction of oxidative stress, inhibition of inflammatory response, immunomodulatory separation of VSMC proliferation and migration [40].

Baicalin has shown protective effects on myocardial infarction in rats. The underlying mechanism may be due to oxidative stress and upregulation of Bcl-2 protein expression and downregulation of DX protein expression in myocardial tissue [41].

13. *Polydatin*

It is a stilbenoid polyphenol also known as piceid isolated from *Reynoutria japonica* Houtt. *Polydatin* poses potential biological activities such as anti-inflammatory, antioxidant, through the modulation of pivotal signalling pathways involved in inflammation, oxidative stress and apoptosis. *Polydatin* reported to exert therapeutic effects against acute myocardial infarction and vascular damage [42].

14. *Oleuropein*

It is a bitter, glycosylated sec-iridoid, a type of phenolic compound, found in olive leaves and oil. It has antioxidant properties, which may help lower blood pressure, inflammation, cardiovascular disease and diabetes [43,44].

15. *Calycosin-7-O-β-D-glucoside*

It is an isoflavone glycoside extracted from *Austragalas mongholicus* medicinal herb. The major biological activities are cardioprotective, anti-inflammatory, antioxidant, and osteogenic. It exerts protective effects on myocardial infarction in preclinical studies using *in-vitro* and animal models. The mechanisms involved are scavenging ROS, reducing lipid peroxidation, enhancing endogenous antioxidant enzymes activity (e.g. superoxide dismutase and glutathione peroxides) inhibiting pro-inflammatory signalling pathway such as NFkB, inhibiting release of inflammatory cytokines, TNF-α, IL-6, IL-1β. The compound regulates apoptosis-related pathways by balancing pro-apoptic (BAX) and anti-apoptotic (BCL-2) proteins. This prevents cardiomyocytes approaches a significant contributing factor to MI induced damage [45–47].

16. *Andrographilis paniculate*

Andrographilis paniculate hydro-alcoholic extract treatment produces restored hemodynamic paradigms and left ventricular function increased the depleted antioxidant enzymes improved the ventricular function and structural integrity of heart cardiac biomarkers enzymes and lipid peroxidation process are significantly decreased. Furthermore, the extraction showed ischemic properties by reducing the size of myocardial infarction, and lessen myocardial fibrosis. The protective effects are attributed to the plant antioxidative scavenging free radical ROS and anti-inflammatory properties, inhibition of NFkB signalling cascade as well as the antioxidant defense system [48].

17. *Allium sativum*

Aqueou garlic homogenate likely phytoconstituents (s-allyl-L-cystein dualkyl 16 diallyl disulfide) treatment doses elevated the depleted SOD, CAT activities and decreased cardiac biomarkers LDH and CKMB in serum. Higher dosage showed significant cardioprotective effect against ISO-induced myocardial damage in rats. The extract treatment restores the depleted endogenous antioxidant enzymes (CAT, SOD levels) significantly thus Allium *sativum* extract significantly reduce the isoproterenol-induced oxidative stress. Thus, phenol and flavonoids of the extracts antagonise the oxidative stress and reduce cardiac damage and the levels of cardiac markers in heart muscle [49].

18. *Acorus gramineus/Acorus calamus*

The genus Acorus belongs to Acoraceae family. The phytoconstituents of Acorus are: terpenoids, phenyl propanoids, beta and alpha asarone. *A gramineus* 500mg/kg treatment orally for 9 days significantly reduced ISO-induced cardiac damage (dysfunction) as reflected in ventricular ST segment interval, R amplitude as well as the LV fractional shorting and ejection fraction. Further activities cTnT, TNF-alpha, MPO and cardiac markers enzymes as well as the levels of MDA are also decreased [50].

The leaf water extract of *Acorus calamus* treatment inhibits the production of pro-inflammatory cytokine IL-8, IL-6 and HaCaT-cells and inhibition has been attributed to Nf-kB activation and phosphorylation IRF3. *A.gramineus* has TH_2 polarisation characteristics and anti-inflammatory property. Beta-asarone (25, 12.5, and 6.25 mg/ml) significantly reduces the ischemia and reperfusion injury of neonatal rat cardiomyocytes induced by $Na_2S_2O_4$ to varied degree (reduced LDH, creatine kinase and protected the structure and function of myocardial cell membranes. Beta-asarone (40 mg/kg)

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decreased significantly level of endothelin and also reduced the degree of myocardial tissue damage and necrosis rate in rats with myocardial ischemia. The mechanism mainly relates to reduction of cell membrane damage and mitochondrial membrane permeability. However, dosage is critical due to toxicity side effects. Beta-aserone (40 mg /kg) prolonged clotting time in mice, reduced the weight of plasma fibrin clots, and prevented platelet aggregation in hyperlipidemic rats. Therefore, it may have a role in the prevention and treatment of thrombotic cerebrovascular disease. Experimental study also demonstrated beta-asarone reduced lipids by inhibiting the expression of adipogenic transcription factor and also suppress adipogenesis and inhibit PPARC expression. *Acorus calamus* exerts therapeutic effect on cardiac ischemia disease, especially through the endothelium-dependent hyperpolarising factor, which is known to regulate coronary vasodilation effect and enhance coronary blood flow. Ethyl acetate extracts of *A.calamus* rhizome (250 mg/kg) to hypertensive rats reduced systolic blood pressure, diastolic blood pressure, serum renin activity, and blood urea nitrogen. Also reduce antioxidant enzymes (glutathione, superoxide dismutase, and catalase). The essential oil of *A. calamus* has shown anti-atrial fibrillation, atrial fibrillation, ventricular arrhythmia, etc. Clinically, it has been assessed that the health status of patients with ischemic heart disease has been improved significantly [51–53].

19. *Panax ginseng (P.genseng)*

Aqueous extract treatment produces decreased MDA myocardial injury parameters and cardiac dysfunction ST segments and QRS complex internal interval. The anti-inflammatory, anti-fibrotic and cardioprotective properties of *Panax ginseng* may be related to the inhibition of NLRP3 inflammosomes and TGFBR/Smads through SIRT1/NFkB signalling pathways. It can prevent it prevent and treat myocardial a r injury for several days Figure 3.

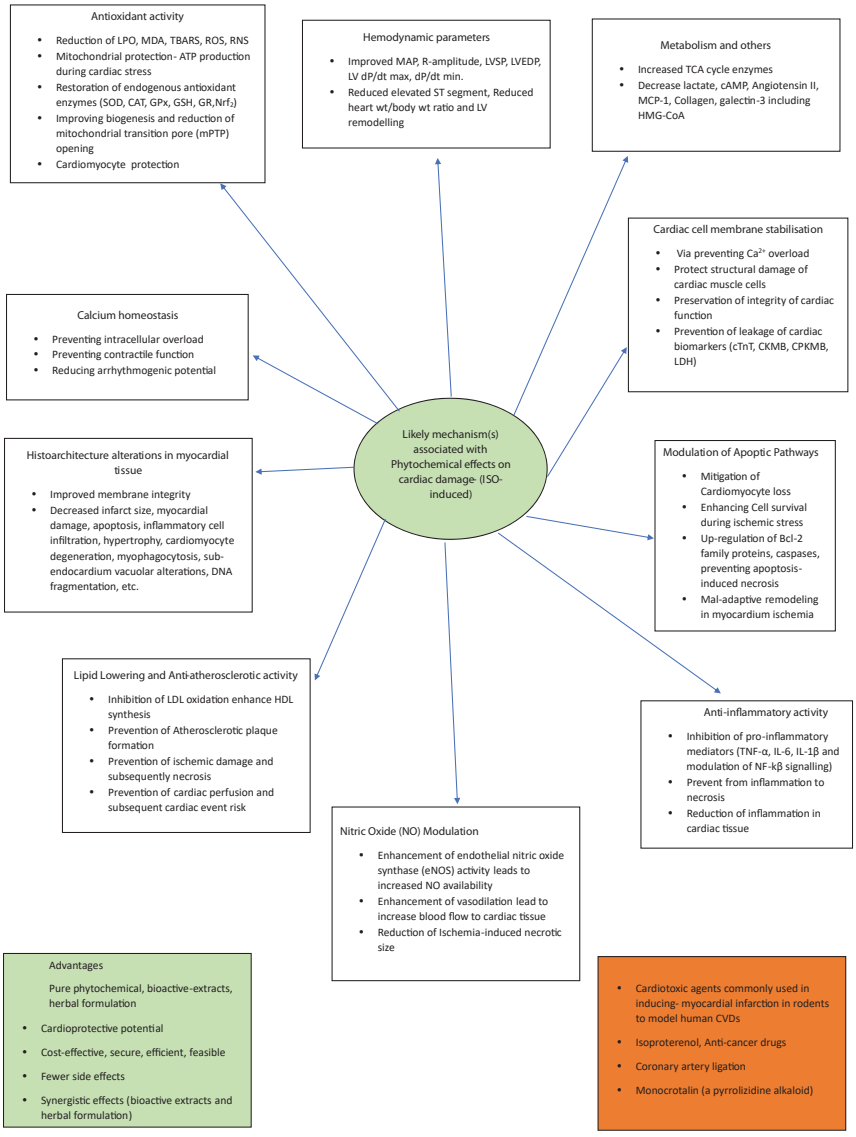

Figure 3: Illustrates protection against ISO-induced cardiac damage by phytochemicals (isolated pure plant constituents, bioactive plant extracts or herbal formulations) via amelioration of various biochemical events associated with oxidative stress, anti-inflammatory activity, and lipid-lowering effect, modulation of apoptotic pathways, calcium homeostasis and hemodynamic alterations. All these effects indicated in the figure are well documented in scientific studies.

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20. *Olea europea*

Orally for 9 days exhibits cardioprotective activity through the methanolic extract with treatment of 500mg/kg. Free radical scavenging reduced MDH level, decrease oxidative stress, ameliorated myocardial injury, its biomarkers, and improved cardi dysfunction, ST segment and QRS complex intervals, restored ventricular hemodynamic functions, decreased sensitive cardiac injury serum markers (e.g. cTnT, CKMP, LDH and attenuated the cardiac remodelling through inhibition of ACE activity [54].

Embelin

Embelin is a major constituent of *Embelia ribes* and has demonstrated cardioprotective properties. In an experimental study, oral administration of embelin at 500 mg/kg for three days before isoproterenol (ISO) treatment significantly decreased the elevated levels of specific cardiac injury biomarkers, including CK-MB and GST. Histological architecture of cardiac tissue was also improved. Furthermore, embelin treatment restored mitochondrial respiratory enzyme activities, including NADH dehydrogenase, succinate dehydrogenase, and cytochrome oxidase, while enhancing mitochondrial redox activity and antioxidant defense systems. Embelin also attenuated ISO-induced myocardial peroxidation and mitigated mitochondrial-dependent apoptosis by upregulating Bcl-2 expression and downregulating Bax, cytochrome C, cleaved caspases-3 and -9, and PARP. Thus, embelin may have potential benefits in preventing cardiac ischemia [55].

Acalypha indica

The extract from *Acalypha indica* leaves, rich in steroids, terpenoids, phenolics, tannins, alkaloids, flavonoids, and saponins, has shown cardioprotective effects. Oral administration of 200 mg/kg of the extract demonstrated protective activity against ISO-induced cardiac ischemia by restoring cardiac serum markers, including LDH, CK-MB, and troponin T, while normalizing lipid peroxidation activity [56].

Paeonia emodi

Commonly known as Himalayan peony, *Paeonia emodi* extract contains phytoconstituents such as ursolic acid, rutin, methyl ursolate, and isophthalic acid. It exhibits cardioprotective activity in an ischemic heart disease rat model by reducing elevated lipid levels, enhancing antioxidant defense, stabilizing cardiac cell membranes, and decreasing AST, ALT, CK, and LDH levels. It also protects DNA and reduces lipid peroxidation [57].

Alkaloids

Alkaloids such as alstonine, vincosamide, vincristine, and coptisine exhibit cardioprotective activity largely through their antioxidant, anti-apoptotic, and anti-inflammatory properties. They contribute to the preservation of myocardial energy metabolism.

Coptisine

Coptisine, a naturally occurring alkaloid found in *Coptis chinensis* (Chinese goldthread) and *Chelidonium majus* (greater celandine), reduces mitochondrial respiratory dysfunction and downregulates the RhoA/ROCK signaling pathway, ultimately reducing apoptosis [58].

Berberine

Berberine, an isoquinoline alkaloid first isolated from *Berberis* species, demonstrates a broad spectrum of pharmacological activities, including hypoglycemic, hypolipidemic, hepatoprotective, anti-inflammatory, and antioxidant properties. It has been shown to exhibit cardioprotective effects by reducing serum biomarkers such as CK-MB, LDH, and troponin I, attenuating oxidative stress, and improving mitochondrial function through the regulation of Bcl-2 and cytochrome C expression [59].

Terminalia arjuna

Terminalia arjuna, a well-known cardiotonic plant, contains active phytoconstituents including flavonoids, polyphenols, tannins, and glycosides. Extracts from its bark exhibit cardioprotective activity by reducing arterial pressure, enhancing platelet regulation, and preventing myocardial damage. Its cardioprotective properties are attributed to its antioxidant effects, inhibition of NF-κB, IL-18, and other cytokines, as well as modulation of PPAR-γ and LXR-α pathways, which enhance the uptake of oxidized LDL and reduce atherosclerotic plaque formation [60].

Silybum marianum

Silybum marianum contains silymarin, a flavonolignan mixture composed of silybin A, silybin B, isosilybin A, and isosilybin B. Silymarin exhibits dose-dependent cardioprotective activity against ischemia-reperfusion injury by enhancing endogenous antioxidant enzymes (SOD, CAT, and GST) and inhibiting NF-κB activation, thereby reducing oxidative stress and inflammatory responses [61].

Rutin

Rutin, a flavonoid found in various plants such as *Fagopyrum esculentum* (buckwheat), tea, and apples, has been shown to exhibit antioxidant, anti-inflammatory, and vasoprotective activities. In ischemia-reperfusion-induced myocardial infarction models, rutin significantly reduces infarct size, scavenges free radicals, attenuates lipid peroxidation, and improves myocardial enzyme activities, contributing to its cardioprotective effects [62]. It is a quercetin derivative, chemically known as quercetin-3-rhamnoglucoside. Rutin improves variation of myocardial zymogram and upregulates antioxidant system in heart. Docking studies demonstrate the key role (SIRT-1) of rutin's cardioprotective effect. It is observed that activation of SIRT-1/Nrf2 signalling induced by rutin participates in the reduction of oxidative stress, along with reduced apoptosis of cardiac cells in the heart tissue. Also demonstrates that SIRT-1/Nrf2 signalling pathway may be an important therapeutic target for the treatment of oxidative stress, apoptosis and related myocardial diseases [63]. Experimental evidence with rutin suggests beneficial effects

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on cardiac remodelling, evidenced by its effects on cardiac structure and function in several cardiac diseases models via multiple pathways [64].

Alpinia zerumbet

Traditionally used in Brazilian folk medicine for hypertension, *Alpinia zerumbet* leaf extract exhibits cardioprotective activity in ISO-induced myocardial infarction models by reducing cardiac biomarker enzymes, infarct size, and histopathological necrosis. The presence of phytoconstituents such as volatile oils, flavonoids, and phytosterols is responsible for its pharmacological effects, including antioxidant and vasorelaxant properties [65].

Coumarins

Coumarins, belonging to the benzopyrone family, are widely present in medicinal plants. They exhibit diverse pharmacological activities, including anticoagulant, antidiabetic, hepatoprotective, and anti-inflammatory effects. Certain coumarins enhance myocardial contractility and reduce oxidative stress, contributing to their cardioprotective potential [66].

TDHKOI

TDHKOI, a traditional Japanese medicine containing nattokinase and other herbal components, has demonstrated cardioprotective effects in ISO-induced myocardial infarction models. It significantly improves electrocardiographic abnormalities, reduces cardiac-specific serum biomarkers, and enhances antioxidant enzyme levels, suggesting its potential as an adjunct therapy for cardiovascular diseases [67].

Morin hydrate

Morin hydrate, a flavonoid derived from the *Moraceae* family, exhibits cardioprotective effects by improving myocardial histoarchitecture, reducing inflammatory biomarkers, and inhibiting apoptosis through the MAPK/NF-κB pathway. It also preserves mitochondrial function and attenuates ischemia-induced myocardial injury [68].

Alpha-terpineol

A major component of the resin of *Protium heptaphyllum*, alpha-terpineol has been used in traditional medicine for cardiovascular disorders. Studies suggest its vasorelaxant and antihypertensive effects, along with cardioprotective properties in ISO-induced myocardial infarction models [69].

Corydalis yanhusuo

Corydalis yanhusuo extract contains tetrahydropalmatine (THP), which exhibits promising effects in myocardial infarction-induced cardiac dysfunction. THP treatment has been shown to reduce infarct size, improve heart function, and inhibit neurohumoral activation. Additionally, it exerts anti-apoptotic and antioxidant effects through the PI3K/Akt/eNOS pathway, enhancing HIF-1α and VEGF expression, and reducing inflammatory mediators in cardiac tissues [70].

Discussion and future perspective

In this review we have referred to many documented plant extracts/phytochemicals, and plant-derived analogues such as phenol, flavonoids, saponin, triterpenpids, alkaloid and derivatives. Herbal formulations having wide therapeutic activity on myocardial ischemia and other related cardiac disorders are complex diseases, and it is only natural to have multi-targeted combination therapy like a formulation of several individual herbal products can effectively counteract such pathological condition. Further, herbal formulation therapies are much better than conventional drugs, being less costly, more eco-friendly, secure, better availability, and acceptable in different cultures and society. All these preparations plant extract phytochemicals plant derived products exerts antioxidant activity, provides maintenance of endogenous antioxidant enzymes (SOD, CAT, Gpx, GST and inhibition of LP) increase initial pharmacological studies in ISO-induced myocardial damage model. Other vital sensitive cardiac biomarkers search as CTnT, CTnl, CKMB, LDH, NO expression and apoptosis have been significantly reduced upon free treatment with these herbal preparations. In addition, plant extract also reduce the elevated calcium ions will ultimately decrease the formation of ROS and free radicals such biochemical effects of these herbal products will lead to reduction infarct size along with the decreased inflammation, necrosis, leukocytes infiltration, DNA damage, degeneration myofibrillar tissue, myocardial hypoxia and hypertrophy. Many herbal products restored ECG and other changes in hemodynamics. The cardioprotective potential of certain plant extracts are aptly supported by both *in-vitro* and *in-vivo* findings. The major drawbacks of phytochemicals plant extracts and Poly herbal formulations reported to be poorly absorbed and do not exhibit a desirable pharmacokinetics profile in humans. These factors are essential for achieving better clinical effects. Also need to work on novel approaches of drug delivery systems such as nanotechnology including nano liposomes, nano suspension, micelle to address poor quality, instability, and thereby improving solubility and absorption by the active compounds [71]. Besides the above-mentioned novel approaches, it may be essential for enhancing pharmacotherapy of phytochemicals researchers need to focus efforts on preparing new generation conjugates with phytochemicals, such piperine, resveratrol, for improving bioavailability, pharmacokinetics features of the active molecules. Also required to develop the state-of-the-art methodology for animal models to be used for the studies, to simulate pathophysiological symptoms, cellular and subcellular, and molecular levels, may provide comprehensive insights into the cellular and molecular impacts of active phytochemical analogues (synthetic and semi-synthetic). The phytochemicals need to be standardised to meet the international quality control standard with proper guidelines and specifications (Figure 4).

CRediT authorship contribution statement

Suresh Naik: Supervision, Conceptualization, Formal analysis, Visualization, original draft, review, editing. Dipesh Gamare: Writing – original draft, review, editing & Visualization.

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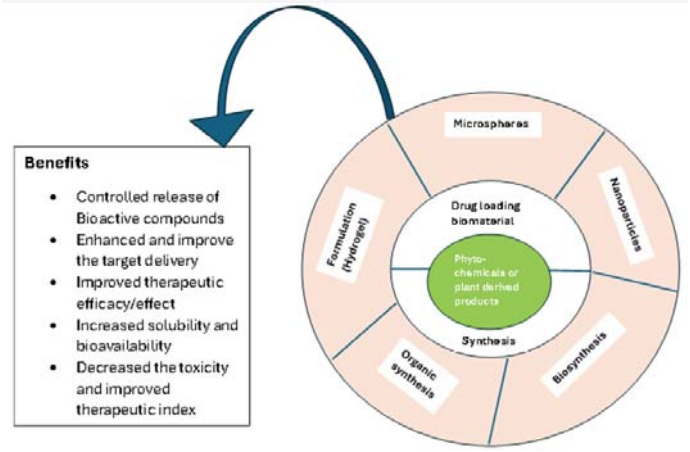

Figure 4: Novel approaches for chemical, structural modification, and functionalization of Phytochemicals/plant-derived analogues and other plant products. Drug-loaded biomaterial (nanoparticles, microspheres, and hydrogels) have been demonstrated to enhance solubility and target natural products mentioned above. These preparations are paramount in drug delivery system (a versatile and sophisticated platform for targeted therapy and controlled release of phytochemicals and natural products) (Adopted from [71] with minor modification).

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