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A REVIEW ON MANAGEMENT OF CARDIOVASCULAR DISEASES BY HERBAL NANOPARTICLES

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ABSTRACT: Cardiovascular diseases (CVDs) are related to heart and blood vessel disorders. The changing lifestyles of unhealthy diets, physical inactivity, and tobacco and alcohol consumption have increased the risk factors of heart diseases. A literature search reveals that the rise in risk of CVD's is higher after a SARS-COV2 infection. Also, CVDs independently are one of the leading cause of death globally. There is hence a need of research of new molecules with improved therapeutics. Herbal medications have been utilized to treat cardiovascular diseases for many years around the world. The advancement of herbal nanotechnology in the field of CVDs has been shown to have astounding benefits over herbal crude drug formulations or herbal extracts, including better solubility, bioavailability, toxicity protection, pharmacological activity augmentation, dose reduction, and stability. This paper discusses the traditional herbal drugs and the herbal formulations, specifically herbal nanoparticles (NPs), for the treatment of CVDs and their advantages.

INTRODUCTION: CVDs are the biggest cause of death worldwide and are expected to continue to be so. Coronavirus disease 2019 (COVID-19), caused by a coronavirus strain known as SARS-CoV-2, has spread worldwide, affecting billions of people. COVID-19 and cardiovascular disease appear to be linked, according to research. Patients with COVID-19 with pre-existing cardiovascular illness had the worst results and were more likely to die, whereas COVID-19 can also cause myocardial damage, arrhythmia, acute coronary syndrome, and venous thromboembolism, which has become a severe concern [1].

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A large number of curative options have been developed for the management of CVDs. The treatment modalities include using different medications like beta-blockers, statins, aspirin, and angiotensin-converting enzyme inhibitors. Other than these medications, surgical operations and medical devices are also preferred to treat CVDs. Rashes, constipation, nausea, sleepiness, edema, low blood pressure, headache, renal failure, and bleeding are all side effects of the medications used in these treatments [2]. Therefore, the demand for herbal drugs over synthetic drugs has increased.

Nowadays, natural products are gaining popularity because they reduce the progression of CVDs and, unlike synthetic medications, have less adverse effects. They are also cost-effective, readily available, and have good therapeutic potential. Still, one of the biggest challenge while using the phytoconstituents is their poor bioavailability and

patient compliance. There is a need to design the proper dosage form for effective therapeutics. This can be accomplished by designing novel drug delivery systems for herbal drugs. Nanoparticles are nano-sized vesicles that can transport therapeutic drugs in a sustained and targeted manner *via* an active or passive target mechanism, resulting in improved myocardial healing in CVDs. Furthermore, it can deliver medications with a longer half-life, lower toxicity, and fewer adverse effects. Nanoparticles are classified as organic, inorganic, and hybrid nanoparticles depending on their synthesis method. Organic nanoparticles are prepared from organic compounds like proteins, carbohydrates, lipids, *etc*. with characteristics dimensions 100nm and are widely used in cardiac therapy. Inorganic nanoparticles again are divided into two types carbon-based nanoparticles and metal nanoparticles; Carbon nanotubes, bulky balls, and graphene are examples of carbon-based NPs with exceptional characteristics, strength, and electrical qualities (conducting, semiconducting, or insulating). Besides, these inorganic NPs also include metal NPs, made of gold, silver, and iron oxide, which are also widely used for cardiac therapy [3].

Curcumin, emodin, gymnemicacid, berberine, quercetin, magnolol, breviscapine, resveratrol, baicalin, naringenin, and other phytochemicals have all been administered via organic and inorganic NPs [4]. But when it comes to CVDs, the information obtained is insufficient. Hybrid nanoparticles combine organic and inorganic nanoparticles, leading to improved physicochemical properties like particle, surface charge, and Polydispersity index, and are promising prospects for CVDs treatment.

This study aims to look at the therapeutic benefits of herbal NPs in the treatment of CVDs. This article outlines medicinal plants and natural products that can help in cardiovascular disease treatment, as well as current breakthroughs in herbal-based nanoparticles as systematic and targeted carriers for drug administration.

MATERIALS AND METHODS: Electronic search engines such as Scopus, PubMed, Google Scholar, authorized articles and Ayurvedic literatures were used to gather information about herbal medicines and herbal NPs used in the treatment of CVDs. Non-English language articles were prohibited in order to unify the data.

Herbal Drugs used in Cardiovascular Diseases: Chemicals produced by primary or secondary metabolism that have therapeutic properties are known as phytoconstituents. Cardioprotective effects were thought to be mediated by carotenoids, triterpenes, flavonoids, cardiac glycosides, alkaloids, saponin, sapogenins, polyphenols, terpenoids, fatty acids, and other secondary metabolites [5]. Medicinal plants such as *Terminalia arjuna* Linn, *Glycyrrhiza glabra* Linn, *Albizia lebbeck* Linn were well known to have cardioprotective potential and found to be the most common plant drugs utilized in the herbal products to treat CVDs. It is reported that *Terminalia arjuna* causes the reduction in myocardial superoxide dismutase, reduces the glutathione, induces the focal dilation of the smooth endoplasmic reticulum causing the positive ionotropic effect, *Glycyrrhiza glabra* induces proliferation of vascular endothelial cells, causes regeneration of the blood vessels; and the *Albizia lebbeck* causes rearrangement of cytoskeleton, improving the contractile function and reperfusion [6, 7, 8].

Terminalia arjuna: *Terminalia arjuna* Linn is a huge evergreen tree that grows to 60 to 80 feet in height. *Combretaceae* is the plant's family. It's primarily found in India's sub-Himalayan regions. The bark has a grey-brown outer coating and a red inside. Flavonoids, triterpenes, tannins, arjunetin, polyphenols, b-sitosterol, arjunic acid, and other phytoconstituents can all be found in the Arjuna plant. Arjuna plant leaves and bark include cardioprotective properties. It is an Ayurvedic medicine referenced in numerous ancient Indian medicinal works, including Charaka Samhita, Sushruta Samhita, and Astang Hridayam, since the Vedic time [9, 10].

T. arjuna alcoholic extract was tested in rats for its cardioprotective effects against isoproterenol-induced myocardial damage; after 4 weeks of treatment with Arjuna extract, the rats were administered with isoproterenol (85 mg/kg body weight, sc.) for 2 consecutive days to all the treated animals to induce myocardial injury. The study's findings demonstrated that *T arjuna* reversed the

ischemic-reperfusion injury caused by isoproterenol, preventing the myocardium from being damaged [11]. In another study effect of aqueous extract of *T. arjuna*on mice model against DOX-induced cardiotoxicity was evaluated. The study concluded that *T. arjuna* aqueous extract has cardioprotective potential [12]. Oxidative stress in myocardial ischemic-reperfusion injury caused raised levels of myocardial thiobarbituric acid reactive substances and depletion of endogenous myocardial antioxidants GSH, SOD, and catalase. On the treatment with *T. arjuna* bark extract, recovery of myocardial function, with a significant reduction in thiobarbituric acid reactive species, and a rise in SOD, GSH, and catalase were observed, concluding cardioprotection against oxidative stress associated with myocardial ischemic-reperfusion injury [13]. Also, in one study, the cardioprotective effects of oral administration of *T. arjuna* against caffeine-induced coronary heart disease was evaluated in male Wistar rats. The study's findings demonstrated that *T. arjuna*'s cardioprotective action is related to its free radical scavenging activity [14]. *T. arjuna* has been proven to improve cardiovascular neuropathy in rats having uncontrolled diabetes, the study included treatment of the rats having diabetic cardiomyopathy with *T. arjuna* extract for 30 days, which resulted in reflex bradycardia generated by rise in arterial pressure was significantly reduced after diabetes but was regained after treatment with *T. arjuna* [15].

Glycyrrhiza glabra: *Glycyrrhiza glabra* Linn is a perennial shrub with a height of about 2.5 m, belonging to the family *Leguminosae*. The roots contains saponin glycyrrhizin, and flavonoids like liquirtin, isoliquertin liquiritigenin and rhamnoliquirilin. Many volatile components identified in roots include pentanol, hexanol, linalool oxide A and B, tetramethyl pyrazine, terpinen-4-ol, - terpineol, and geraniol. *G. glabra* was reported to have a cardioprotective effect against ischemia-reperfusion injury (I-R) in rats [16].

The cardioprotective potential of *G. glabra* was investigated through human umbilical vein endothelial cells (HUVECs) and transgenic zebrafish. The study concluded that isoliquiritin (ISL), the flavonoid derived from the licorice roots, have counteracted tyrosine kinase inhibitor II (VRI)-induced endothelial cell apoptosis and promoted cell migration and tube formation in HUVECs. ISL markedly activates vascular endothelial growth factor receptor-2 (VEGFR-2), phosphoinositide 3-kinase (PI3K), Raf and mitogen-activated protein kinase (MEK)-dependent signaling pathways, thus causing the pro-angiogenesis [17]. The cardioprotective impact of *G. glabra* on diabetic myocardial damage was investigated. The diabetic heart showed considerable changes in gap junction protein connexin-43 (CX43), cardiac injury marker troponin I, and cardiac muscle-specific voltage-gated sodium channel NaV1.5. Additionally, the diabetic heart contained greater concentrations of the inflammatory mediator phospho-p38 MAPK, the chemokine receptor CXCR4, the oxidative stress mediator receptor for advanced glycation end-products (RAGE), and the mediator of oxidative stress. The expression of phospho-p38 MAPK, RAGE, NaV1.5, and TGF- was reduced after treatment with *G glabra* extract, as was the expression of CX43, CXCR4, Nrf2, and troponin I, suggesting that *G. glabra* has cardioprotective effects in diabetic cardiac atrophy, which could be mediated through activation of Nrf2 and inhibition of CXCR4/SDF1 as well as the TGF-/p38MAPK signaling pathway [18].

In one of the other study for evaluating the cardioprotective effect of *G. glabra*, myocardial ischemia injury was induced to the rats by administering ISO (85 mg/kg) subcutaneously for 2 consecutive days. On the treatment with Monoammonium Glycyrrhizinate (MAG) injection, reduced damage, improved cardiac morphology, inhibited oxidative stress, decreased generation of reactive oxygen species, and decreased intracellular Ca2+ concentration was observed which indicates the cardioprotective influence of MAG injection [19].

Albizia lebbeck: *Albizia lebbeck* Linn is a fast-growing medium-sized deciduous tree belonging to the family *Mimosaseae*, with a height growth ranges from 0.5- 2m. It has a spreading umbrella-shaped crown of thin foliage and fissured greyish-brown bark.The bark consists of condensed tannins, catechins, an isomer of leucocyanidin, melacacidin, bita-sitosterol, betulinic acid, and its gylcosides, *Albizia saponin* A, B, C, and phenolic glycoside albizin. The cardioprotective and antioxidant potential of *A lebbeck* was investigated by DPPH

assay, and it was concluded that DPPH gives an absorption band at 517nm; when an off electron pairs with the scavenger, the absorption band reduces, which indicates the antioxidant activity, which is dose-dependent [20]. In one of the other studies three flavonoids, (1) 5-deoxyflavone (geraldone), (2) luteolin and (3) Isookanin were isolated from *A lebbeck* bark. *In-vitro* research linking the antioxidant and cardioprotective properties of all the phytoconstituents demonstrated all of them to block the -glucosidase and -amylase enzymes [21].

Curcuma longa: Cardioprotective potential of *C. longa* was investigated by recording Haemodynamic parameters, heart rate, left ventricular end-diastolic pressure, cardiac marker enzymes level, histopathological examination of heart tissues, *etc*.

Significant myocardial necrosis, reduction in cardiac function, increase in lipid peroxidation, and the antioxidant status of the rats were all detected after ISP induction. When given orally to healthy experimental animals, *C. longa* dramatically increased the basal levels of GSHP x and CAT activity when compared to the control group. After ISP-induced myocardial injury, pretreatment with *C. longa* (100 & 200 mg/kg) for 30 days had significant mitigating effects on a number of the biochemical and histological alterations brought on by myocardial injury. According to the findings, continuous *C. longa* treatment induces myocardial adaptation by increasing endogenous antioxidants and shields rat hearts against oxidative stress and a loss in cardiac function brought on by ISP-induced myocardial injury [22].

Tribulus terrestris: *T. terrestris* have been reported to have excellent cardioprotective activity, which was evaluated on albino wistar rats. In one of the study, the rats were divided in normal control, *T. terrestis* extract alone treated, ISO control, and pretreated (*T. terrestris* extract +ISO) groups. Rats were induced with ISO leading to myocardial infarction (MI), causing a disturbance in serum lipid profile and antioxidant levels. Upon treatment with extract, had significantly showed a protective effect against ISO-induced myocardial damage in the rats [23]. In a different investigation, the effectiveness of *T. terrestris* methanolic extract against cardiac ischemia was assessed using *in-vivo* (Wistar rats) and *in-vitro* (H9c2 cell line) models of myocardial ischemia. ECG and other cardiac biomarker analyses showed that *T. terrestris* was effective against myocardial ischemia in the rat. It was discovered that it functions by blocking the mitogen-activated signaling pathway, preventing apoptosis during ischemia injury [24].

Bacopa monnieri: *B. monnieri* has shown good results in maintaining cardiac rhythm and myocardial integrity and decreasing oxidative stress by strengthening the endogenous defense system through Nrf2 modulation [25]. Additionally, *B. monnieri* has been shown to increase coronary flow by 63% (30 g/ml) and 216% (100 g/ml), compared to control (5%) making it the perfect treatment for ischemia/reperfusion injury. *B. monnieri* (100 g/ml) was also said to have decreased the percentage of infarct size from 51% (control) to 25% [26].

Withania somnifera: Doxorubicin was reported to have a potent antineoplastic activity, and it is limited to cardiotoxic effects. Increasing malondialdehyde and protein carbonyl levels and catalase activity produces oxidative stress damage. This leads to the concomitant depletion of total antioxidant capacity and of superoxide dismutase level in cardiac tissues. Upon treatment with *W. somnifera* extract, the increase in AST levels attenuates the damage caused by protein and oxidative stress. This antioxidant effect of *W. somnifera* extract was thought to be attributed to the presence of steroidal lactones, withanolides, which represent the main active component of *W. somnifera* [27].

Zingiber officinale: Ginger was also referred to as the omniscient medicine that can be administered to anyone living in this world, and it would be suitable to all. It has been reported to have astounding benefits in managing and restoring CVDs, including hypertension, obesity, atherosclerosis and hypolipidemia. *Z. officinale* treatment in case of hypertension and high cholesterol have showed improvement in systolic and diastolic BP by 1 month resulting in decreased hypertension, decrease in the levels of ALT, AST activities & decrease in TGs and TC levels were

reported to be attributed to the Gingerols and shogaols [28, 29].

Garcinia indica: Elevation of biomarker enzymes such as CK-MB, LDH and CK-NAC in serum was observed due to the leakage from heart caused by ISO- induced necrosis. *G. indica* has been reported to protect myocardium by scavenging reactive free radicals and reducing their permeability to nearby cardiac areas. In the histopathological studies of the heart tissue myocardial edema and separation of fibers with loss of striation were seen in myocardial injury, which were ameliorated with treatment of *G indica* extract. It was reported that this cardioprotective activity of the *G. indica* was attributed to the bioflavonoids and tannins present in the extract [30].

Embelica ribes: An aqueous *Embelica ribes* extract pretreatment showed cardioprotective properties in rats by reducing myocardial damage and boosting antioxidant defence against ISO-induced myocardial infarction [31].

Cinnamomum tamala: A lack of oxygen or glucose can harm the myocardial cell membrane, increasing permeability and even rupturing it, which allows the enzyme to escape. These enzymes, which are often referred to as particular biomarkers, can be used to quantify the damage. Compared to the usual, doxorubicin elevates CPK, LDH, ALT, and AST levels. These enzyme levels were reduced after treatment with an ethanolic extract of *C. tamala* leaves at a 400 mg/kg dose, demonstrating the extract's protective or membrane-stabilizing impact on the myocardium. The free radical scavenging and antioxidant activity of the extract, which in turn offers cardio protection, may be caused by the presence of tannins, flavonoids, and alkaloids [32].

Trichopus zeylanicus: According to reports, *T zeylanicus* pretreatment lowers the level of plasma and cardiac lipid peroxides by inactivating the enzyme cyclo-oxygenase and appearing to scavenge superoxide and hydroxyl radicals in isoproterenol-induced myocardial infarction directly. Further research revealed that pretreatment with *T. zeylanicus* extract raised the levels of cardiac-specific proteins like troponins as well as blood enzymes like CK, LDH, AST, and ALT, demonstrating the herb's stabilizing effect on myocardial infarction, which was thought to be attributed to the Alkaloids, glycosides, flavonoids, steroids, and tannins present in the extract of *T zeylanicus* [33].

Cichorium intybus: According to the reports, aging causes peroxidative damage leading to increased malondialdehyde, taurine, and glutathione levels in the heart. Also, the catalase activity decreases upon pretreatment with the dried powdered leaves of *C intybus* it was found that the herb ameliorates the aging-induced injury on the myocardium of albino rats [34].

Daucus carota: The major therapeutic medications used to treat congestive heart failure are cardiac glycosides and catecholamine; however their long-term efficacy has been questioned due to well-known risks associated with cardiac glycoside overdose. The inability of catecholamines to distinguish between their positive ionotropic and chronotropic effects, their potential arrhythmogenic qualities, and their receptor down-regulation-related tachyphylaxis restrict their use. There have been reports that, according to the cardiac enzyme profile, *D carota* extract showed inotropic-like action, which was evident from a general decrease in the activity of Na+K+ATPase and Mg2+ATPase and an increase in Ca2+ATPase, this action was found to be similar to the action of cardiac glycosides.

In one study of isoproterenol induced myocardial damage in rats, increased levels of thiobarbituric acid were reported, indicating the activation of lipid peroxidation and damage to the heart. After the treatment with *D carota* extract, it was found that there had been a decrease in the serum marker enzymes; this antioxidant property was thought to due to the presence of carotenoids in the extract [35].

Cocos nucifera: It has been reported that in an isoproterenol-induced myocardial infarction, there is lower uptake of palmitic acid and its oxidation to CO_2. Coconut protein was reported to exhibit a cardioprotective effect by increasing the concentration of ATP, which in turn increases the ability of the heart to oxidize the fatty acids, and also decreases in the levels of glutamate oxaloacetate transaminase (GOT), glutamate

pyruvate transaminase (GPT) were reported. This cardioprotective activity of coconut protein was claimed to be attributed to the higher L-arginine content. Hence it was concluded that the coconut protein provides cardioprotection by L-arginine nitric oxide pathway [36].

Pithecellobium dulce: In one of the reported studies of isoproterenol (2mg/kg) induced myocardial infarction in male albino wistar rats, it was observed that the pretreatment with the aqueous and alcoholic extracts of *P Dulce* positively altered the activities of serum marker enzymes like SGOT, SGPT, CPK and LDH [37].

Andrographis paniculata: Cardioprotective effect of *A. paniculata* was investigated in one of the study against ISO induced myocardial infarction in rats. It was noted that isoproterenol raised left ventricular end diastolic pressure while decreasing mean arterial pressure, heart rate, contractility, and relaxation; it also increased the levels of serum cardiac injury markers which was restored upon the pretreatment with *A. paniculata* extract (100, 200 or 400 mg/kg) [38].

Ocimum sanctum: In one of the studies against ISO (200mg/kg)-induced myocardial infarction, the impact of *O sanctum* on serum marker enzyme levels and the histology of the heart was examined. The regulation of several antioxidant parameters, suppression of lipid peroxidation, enhancement of SOD activity and improvement in GSH levels by *O. sanctum* (50mg/kg) appears to be the cardioprotective mechanism, increasing the cardiac tissue's overall antioxidant defence [39].

Moringa oleifera: The cardioprotective effect of *M oleifera* (200mg/kg) was evaluated in one of the isoproterenol (85mg/kg) induced myocardial infarction in albino Wistar male rats.

It was reported that restoration of the myocardial SOD, CAT, and GSHPx enzyme activity, leakage of myocardial CK-MB and LDH enzymes were occurred in the *M. oleifera* treated groups of the rats. This cardioprotective property was thought to be attributed to the presence of niazirin, niazirinin, niaziminin A, niaziminin B, moringine and moringinine, polyphenols, tannins, saponins, and phytates [40].

Crataegus oxyacantha: The cardioprotective efficacy of *C oxyacantha* on anti-myocardial ischemia-reperfusion injury effect of resistance training on diabetic rats was reported in one study. Wherein 50 male Wistar rats were split into five groups: sedentary control, sedentary diabetic, resistance-trained diabetic, diabetic plus *C. oxyacantha* extract treatment, and resistance-trained diabetic plus *C. oxyacantha* extract treatment. The rats were treated with *C. oxyacantha* extract (100mg/kg) every day for 10 weeks; after the treatment the rats were subjected to ischemia by artery ligation followed by reperfusion. Later the heart was collected and examined for the levels of cardiac marker enzymes, it was reported from the studies that *C. oxyacantha* treatment group decrease ischemia-reperfusion injury, and this mechanism was thought to be because of the antioxidant property of the extract [41].

Callistemon lanceolatus: The cardioprotective effect of ethanolic extract of *C. lanceolatus* was studied on the doxorubicin-induced cardiomyopathy in the rats. It was reported that the extract of *C. lanceolatus* (200 mg/kg) was used as a co- and pretreatment. It was found to significantly increase tissue antioxidant levels while lowering malondialdehyde levels (p 0.01) compared to the control. It also significantly reduced the elevated levels of serum enzymes and restored normal blood pressure and ECG. Systolic, diastolic, mean blood pressure and heart rate are all reduced by doxorubicin. Additionally, it was noted that the myofibrils are disrupted by doxorubicin, which lowers systolic, diastolic, mean blood pressure, and heart rate while restoring them to nearly normal levels with the *C. lanceolatus* extract [42, 43].

Psidium guajava: The medicinal herbs with radical scavenging activity were evaluated for their cardioprotective effect against ischemia-reperfusion injury using isolated perfused rat hearts. The effect of *P. guajava* aqueous extracts on ischemic reperfusion injury was compared with Quercetin and Gallic acid. The plant extract was reported to reduce the increase in high-energy phosphates and the decrease in malondialdehyde. It was further concluded that the plant extract has the equipotent activity of the Quercetinand Gallic acid [44].

Olea europaea: The cardioprotective effect of *O. europaea* (6 and 12ml/L) was evaluated against the doxorubicin-induced cardiomyopathy (30mg/kg). It was reported that Doxorubicin causes an increase in the serum cardiac marker enzymes, indicating tissue injury. After the co-treatment with *O. europaea* extract, it was found that there is a decrease in the serum troponin I and urea levels, also there was a decrease in the malondialdehyde, diene conjugate, and protein carbonyl levels, which indicates the cardioprotective effect of *O. europaea* by lowering the oxidative stress and decreasing the nitric oxide synthase. This herb property was expected to be due to the presence of flavonoids, iridoids, secoiridoids and benzoic acid derivatives in the extract [45].

Allium cepa: To study the cardioprotective effect of *Acepa* on isoprenaline-induced myocardial injury in Wistar albino rats, they were treated with *A. cepa* extract 400mg/kg and 800mg/kg, and myocardial injury was produced using isoprenaline injection (85mg/kg). *A. cepa* extract showed significant antioxidant activity by lowering the levels of Troponin-I, Creatine kinase, glutamate-pyruvate transaminase, HR, R-R interval, and oxidative stress markers. During the study, it was found that the *A. cepa* extract of 400mg/kg showed significant cardioprotective activity but 800mg/kg dose did not show significant activity hence it was reported and concluded that *A. cepa* has cardioprotective activity at certain dose ranges [46].

Hydrocotyle asiatica: Cardioprotective effect of *H. asiatica* was evaluated on Ischemia-reperfusion induced myocardial infarction in rats, it was reported that the ethanolic extract of *H. asiatica* significantly reduced the cardiac necrosis in dose-dependent manner (100-100mg/kg) by reducing the lipid peroxidation and increasing the glutathione levels thereby producing free radical scavenging activity [47].

Lagenaria siceraria: To investigate cardioprotective effect of *L. siceraria* extract (400mg/kg), isoproterenol (200mg/kg) induced myocardial infarction in rat's model was used. There was a reported decrease in the levels of tissue K+ ion, and the activities of Na+/K+-ATPase and mg+ 2-ATPase thereby providing the proper contraction and relaxation of the cardiac muscles due to maintaining the normal levels of the ions inside the myocyte. These effects were expected due to the presence of polyphenolic compounds in the extract of *L. siceraria* [48].

Crocus sativus: The cardioprotective effect of *C sativus* was studied on the isoproterenol-induced myocardial infarction, and it was reported that saffron and saffranal produced the cardioprotective effect via free radical scavenging activity, thereby reducing the levels of serum cardiac markers and reducing the myocardial lipid peroxidation [49].

Semecarpus anacardium: To evaluate the cardioprotective effect of S*anacardium* nut ethanolic extract, isoproterenol-induced cardiac infarction using Wistar rat's model was used. The cardio markers, antioxidants, and electro-cardiographic parameters were evaluated. Compared to the isoproterenol group, all treatment groups had significantly lower serum levels of thiobarbituric acid reactive species, elevated superoxide dismutase and catalase activities, and decreased lactate dehydrogenase and creatinine phosphokinase-MB activities in the heart tissue, providing cardioprotection [50].

Herbal Nanoparticles as a Novel Approach for Cardiovascular Disease Drug Delivery: Numerous delivery strategies are available for administering therapeutic products for the treatment of CVDs, mainly including the direct intramyocardial injection or intracoronary catheterization. But both techniques can cause severe heart damage and embolization. Hence systemic and targeted intravenous administration of the drug was supposed to be the better alternative. Still, non-functionalized medications cannot target the heart and get removed by the reticuloendothelial system. Therefore encapsulation of the therapeutic drugs inside the nanoparticles can increase the rate of targeted delivery as well as long-term retention at the site of myocardial infarction. So, many literatures have been reported on the *in-vivo* studies of nanoparticles, which have shown the major potential of nanoparticles in improving the functions and regeneration of the diseased cardiomyocyte. Hence, it can be proved that the delivery of the nanoparticles and their therapeutic effects can be achieved by preparing these nanoparticles using heart-targeting active

molecules. The selective targeting agents are MMP-2, MMP-9 targeting peptides, atrial natriuretic peptide, CSTSMLKAC, and CRSWNKADNRSC peptides which have shown increased efficacy, increased half-lives of the drugs compared to the free-form [51].

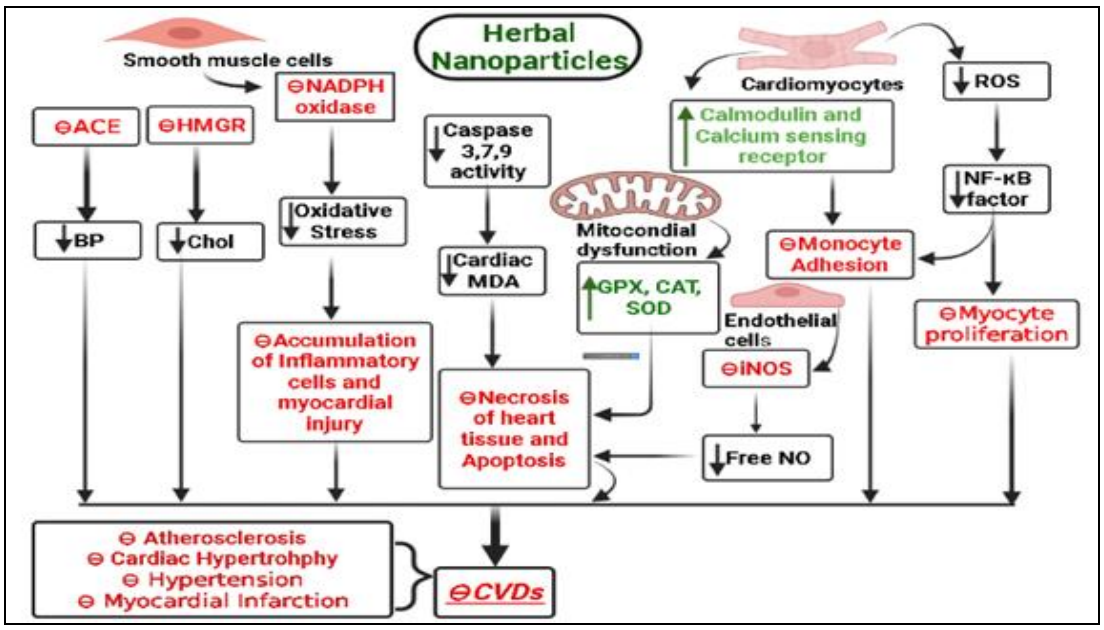

FIG. 1: THE TARGETED MECHANISM OF ACTION OF HERBAL NANOPARTICLES

Considering the continuously growing cases of CVDs, so many scientists and researchers are now interested in developing herbal NPs with validated safety and efficacy. The next sections go over the qualities of herbal-NPs that have been used for the treatment and prevention of CVDs. **Table 2** lists the physicochemical parameters of NPs loaded with various herbal medicines to treat CVDs.

TABLE 1: PHYSICOCHEMICAL PROPERTIES OF NPS LOADED WITH VARIOUS HERBAL DRUGS FOR CVD TREATMENT

Nanoparticle formulation	Zeta potential (mV)	Average size (nm)	PDI	Encapsulation efficiency (%)	Ref
Dracocephalum moldavica L. TFDM-SLNs	−28.7±1.94	104.82±0.24	0.21±0.97	Luteolin 83.98±1.05, rosmarinic acid 87.01±0.83, and tilianin 82 ±0.58 of TFDM-SLNs formulation.	52
Syzygiumcumini Ag NPs	−19.6 ± 0.5	~40–100	0.11±0.87	-	53
Puerarin RGD/PEG-PUE-SLN	−26.2±1.8	110.5±3.4	0.23±0.03	85.7±2.7	54
Quercetin-loaded PLGA	-	343.5±25.4	0.33±0.83	-	55
Baicalin BN-PEG-NLC	−32.1±1.8	83.9±1.6	0.21±0.06	83.5±1.2	56
Magnolol NPs	-	75.6±1.7	0.241±0.023	~96.4	57
Tanshinone IIA-NP	-7.12 ± 0.07	100–200	<0.25	61.30 ± 1.96	58
Resveratrol RSV-NC	−7.15± 0.19	207±0.03	0.12±0.04	99.54±1.02	59
Epigallocatechin- 3-Gallate, L-Enano	−21.81 ± 1.18	104.8±0.4	0.18±0.020	~96	60
Curcumin-loaded PEG-PDLLA NPs	0.44±0.018	57.09±4.52	0.19	82.3±3.71	61
Cherry extract-loaded quaternary ammonium chitosan nanoparticles	14.8 ±0.3	344.9 ± 17.8	0.52 ± 0.08	78.4 ± 4.5	62
Cherry extract- PLGA NP + CE 100	−11.0±1.23	216.0 ± 2.6	0.06 ± 0.03	-	63
PLGA NP + CE 250	–10.9±1.04	216.8 ± 4.9	0.06 ± 0.02	64.8 ± 2.3	
PLGA NP + CE 420	–12.6±0.87	208.4 ± 4.9	0.05 ± 0.02	43.9 ±4.6	
PLGA NP + CE 840	–8.36±1.07	206.1±1.8	0.06 ± 0.03	79.8 ± 6.2	
Ginsenoside P- Rg3	-	49.44 ± 0.15	0.339±0.001	96.47 ± 1.92	64

Lipid nanoemulsions containing Naringenin	-	200	0.2	-	65
Glycyrrhizin alginate nanoparticles	-	50	-	-	66
Baicalin	−32.1±1.8	83.9±1.6	0.21±0.06	83.5±1.2	67
Magnolol encapsulated in EPC (0.01 mg/mL), magnolol encapsulated in DPPC (0.01 mg/mL)	74.13±1.86 64.26±2.92	54.7 27.5	- -	74.13±1.86 64.26 ±2.92	68
Nyctanthus arbor-tristis ZnO NPs	-	~50	-	73.13±2.86	69
Paeoniaemodi AuNPs	−14.38 ± 0.45	203.4 ± 4.72	0.32 ± 0.01	85.23±1.86	70
Moringaoleifera AgNPs	-	~40	-	-	71
Albizia lebbeck Zinc oxide nanoparticles	-	45	0.21 ± 0.16	-	72
S. miltiorrhiza AgNPs	-	120	0.313	-	73
*Terminalia arjuna*AuNPs	-	20–50	-	-	74
Suaeda Monoica AuNPs	-17.15± 0.40	~100	0.287	87.66±0.86	75
*Cassia fistula*AuNPs	-	55.2–98.4	-	-	76
Averrhoabilimbi Fruit Extract AuNPs and AgNPs	-14.23 ± 0.45	50 to 175 AuNPs, 75 to 150 AgNPs	-	-	77

Abbreviations: Total flavonoid extract from D. moldavica solid lipid nanoparticles is referred to as TFDM-SLNs; silver nanoparticles (AgNPs); poly lactic-co-glycolide (PLGA); baicalin-loaded PEGylated nanostructured lipid carriers (BN-PEG-NLC); curcumin-PEG-PDLLA, curcumin-poly(ethylene glycol) methyl ether-block-poly(D,L-lactide); P-Rg3, Rg3-loaded Pluronic F127 micelles; 1,2-diacyl-sn-glycero-3-phosphocholine (EPC); DPPC stands for 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; Gold nanoparticles (AUNPs).

Curcumin: Curcumin has been shown to have antioxidant properties and to protect against oxidative stress-related damage. Curcumin Nano emulsion's antihypercholesterolemic and antihypertensive properties were investigated *in-vitro* utilizing acetylcholinesterase and 3-hydroxy-3-methylglutaryl coenzyme A reductase assay in one of the investigations.

Compared to pure curcumin, Nano emulsified curcumin had a modest increase in inhibitory effect on ACE. Curcumin Nanoemulsion also boosted HMGR inhibition, indicating that it has antihypercholesterolemic properties. Curcumin encapsulated in poly (glycidyl methacrylate) nanoparticles alone and curcumin in combination with a peptide targeting the -interacting domain of L-type Ca2+ channel were tested against ischemia reperfusion injury in rat hearts in another investigation.

Another study found that encapsulating curcumin in carboxymethyl chitosan NPs increased its bioavailability, maintained its bioactivity, and reduced cardiac hypertrophy in rats. Cardio protection was better with the greatest dose of Cs and nC (200 mg/kg bw) [78].

***T. arjuna* Extract:** *T. arjuna* AuNPs neuroprotective potential was assessed using antioxidant, cholinesterase inhibitory, and antiamyloidogenic properties. AuNPs inhibited acetylcholinesterase and butyrylcholinesterase dose-dependently, with IC_{50} values of 4.25 0.02 and 5.05 0.02 g/ml, respectively. AuNPs displayed the best reducing power and DPPH radical scavenging performance in *in-vitro* antioxidant experiments [79]. There was a substantial drop in Red Blood Cells (RBCs), Hemoglobin, Hematocrit, Lymphocyte percentage, and Platelet Distribution Width in acetaminophen-treated Wistar rats, but significant increases in WBC, RBC Distribution Width, and Platelets with acetaminophen treatment. The haematological abnormalities were effectively recovered when green generated AuNPs from *T arjuna* extract were combined with acetaminophen [80].

Quercetin: Quercetin, a flavonoid isolated from *T arjuna*, exerts significant antioxidant, anti-inflammatory, and antihypertensive activities [81, 82, 83]. Quercetin-loaded phosphatidylcholine liposomes (PCLs) were found to protect against peroxynitrite-induced myocardial injuries in both anaesthetized

animals and isolated tissues by acting as a direct scavenger and decomposer of endogenously formed peroxynitrite ions, restoring normal myocardial contractility [84]. In hypoxia-reoxygenation circumstances, administration of quercetin-loaded NPs was also observed to preserve mitochondrial activity and ATP generation, which was related to the suppression of oxidative stress [85].

Glycyrrhizin: Glycyrrhizin is the active constituent of *Gglabra.* The combination of glycyrrhizin and doxorubicin delivered by alginate nanogel particles reduces macrophage activation, decreasing the phagocytosis of macrophage. Also it enhances the bioavailability of doxorubicin.

The anticancer molecular mechanism of glycyrrhizin and doxorubicin combination therapy in ALG NGPs was achieved by regulating the apoptosis pathway of Bax/Bcl-2 ratio and caspase-3 activity, which was also confirmed in H22 tumor-bearing mice, indicating therapeutic efficacy for hepatocellular carcinoma [86].

In one of the other investigations, inflammation mediators such as NO, PGE2, TNF-, and IL-6 were investigated utilizing lipopolysaccharide (LPS)-stimulated murine macrophages RAW 264.7 as an in vitro inflammatory model. LPS elevated these indicators, which were suppressed dose-dependently by nano-GG and unprocessed GG, particularly PGE2 and TNF-. GG nanoparticle suspensions were discovered to have significantly better anti-inflammatory properties than untreated GG [87]. One study looked at the impact of liposome-encapsulated glycyrrhizin on STZ-induced diabetes and the oxidative stress that results in heart damage. Control, diabetes, diabetic treated with free glycyrrhizin, empty liposomes, and liposome-encapsulated glycyrrhizin. Serum glucose, insulin, the intraperitoneal glucose tolerance test, and glycohemoglobin were all calculated. Researchers looked at the effects of free iron and iron-mediated oxidative stress. Treatment with Liposomal-glycyrrhizin alleviated hyperglycemia and glucose intolerance, according to the findings. Liposomes were found to have a greater inhibitory effect than free glycyrrhizin. Diabetes problems were avoided owing to the antioxidant effects of liposome-encapsulated glycyrrhizin treatment [88].

Baicalin: Baicalin, has been demonstrated to have anti-inflammatory and antioxidant properties. Many inflammatory chemokines and cytokines have been found to be suppressed by baicalin. It has been used to treat diabetes and cardiovascular disease [89, 90]. In an acute myocardial infarction model, baicalin-loaded PEGylated nano-structured lipid carriers increased plasma circulation time, improved distribution to the ischemic part of the heart, and reduced infarct size. These nanoparticles has been proposed as a biocompatible carrier for baicalin medication delivery to the heart [91, 92].

***A. lebbeck* Extract:** The antioxidant activity of *A lebbeck* Zinc oxide nanoparticles (ZnO NPs) was investigated using the H2O2 free radical scavenging assay, which indicated IC_{50} values of 48.5, 48.7, and 60.2 g/mL for 0.1M, 0.05M, and 0.01M, respectively. Also, in a concentration-dependent manner, biosynthesized ZnO NPs displayed substantial lethal effects on MDA-MB 231 and MCF-7 breast cancer cell lines (P 0.001, n3), demonstrating the strong antioxidant activity of ZnO NPs [93].

Several approaches, including suppression of the -amylase enzyme and glucose uptake by yeast cells, were used to test the green-produced ZnO NPs for anti-diabetic efficacy and associated cardiovascular effects *in-vitro*. *A lebbeck*, ZnO NPs, and acarbose, with IC_{50} values of 4.91, 9.61, and 3.91, respectively, showed maximum amylase inhibition of 73.33 percent, 54.66 percent, and 46.66 percent in amylase enzyme activity. The glucose uptake by yeast cells was discovered to be dose-dependent and directly proportional to the sample concentration in a glucose uptake experiment. At a concentration of 1 g/ml, the synthesized ZnO NPs were found to enhance glucose absorption by 89.16 % compared to the *A. lebbeck* bark extract and Metformin. Also synthesized ZnO nanoparticles showed more potent DPPH scavenging activity with inhibition 66.66% and IC_{50} value of 7.038. The study revealed the antidiabetic activity of ZnO NPs was due to the radical scavenging mechanism [94].

CONCLUSION: WHO claims that cardiovascular diseases are a major cause of death. 17.9 million people worldwide die from CVDs yearly or 31% of all fatalities. More than 22.2 million individuals are

expected to die annually from CVDs by 2030. Cardiovascular health, prevention, and treatment concerns have increased in response to the SARS pandemic [95]. It is a well-known statistic that approximately 75% of people utilize natural products because they think they are safer than modern treatment. The therapeutic potential of numerous herbal components against CVDs has been discovered through a literature review.

Herbal medications are promising possibilities for the treatment of CVDs because of their low side effects, antioxidant, and anti-inflammatory properties. The primary goal of herbal nanoparticle formulation is to improve the physicochemical qualities of herbal medications by ensuring efficient, regulated, and targeted distribution of the drugs to the site of action. The current study examines the potential therapeutic benefits of herbal NPs for the treatment of CVDs and recent advances in nano phytomedicines.

As previously stated, herbal nanoparticles have a far higher efficiency than traditional formulations. Many herbal nanoparticles and nanoformulations have been used and studied *in-vitro* and *in-vivo* to combat CVDs. *In-vivo* studies have demonstrated that nanoparticle systems have a high potential for increasing damaged myocardium's function and tissue regeneration. However, their therapeutic applications are still in the works, and it is required to figure out how to incorporate the findings of these investigations into clinical trials. The present review attempts to evaluate the relative significance of herbs in regulating heart and cure related diseases. This review could help in drug discovery.

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