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THE EFFECTIVENESS OF BERBERINE AS A THERAPY FOR CARDIOVASCULAR DISEASE

Kavana SM, Dr Beny Baby, Dr S Rajarajan, Amaramma, Krupa N

M Pharmacy, Professor and HOD, Professor and HOD, M Pharmacy, M Pharmacy

Karnataka college of pharmacy

ABSTRACT

The vast majority of research in cardiovascular nanomedicine has concentrated on creating customized nanoparticles for enhanced targeting in order to get beyond biological obstacles. The majority of current cardiovascular diseases (CVDs) treatment approaches concentrate on symptom relief, with just a minimal effect on the underlying physiopathological causes. New developments in technology have enabled the creation of several nanoparticles that are utilized for targeted medicine delivery as well as the diagnosis of cardiovascular disorders. Utilizing nanoformulation techniques enhances these drugs flow time, dissolved state, bioavailability, area-to-volume ratio, potential systemic side effects, and effectiveness of drug administration. The goal of this research was to evaluate how well-suited the newest nanoformulated natural products and/or medicinal plants are to treating different cardiovascular diseases such myocardial infarction, hypertension, atherosclerosis, and thrombosis. The uses and medicinal effectiveness of organic and plant nanoformulations were enhanced through conjugation, combination therapy, or the creation of nanoparticles and nanocarriers. Existing research indicates the plant-based nanoformulations, either by themselves or in conjugation with additional pharmacological or synthetic medications, are remarkably effective in the context of CVDs prevention and/or treatment.

Key words: cardiovascular diseases, nanoparticles, Nano formulation, natural products, medicinal plants

INTRODUCTION

Globally, over seventeen million mortality worldwide are caused by cardiovascular illnesses in 2015; by 2030, that number is expected to rise to twenty-three million. According to The world health organization's 2017 list of coronary heart diseases includes deep vein thrombosis, pulmonary embolism, and myocardial infraction [MI], among others. These conditions cause tissue death and ischemia. Coronary hearty diseases and ischemia are the leading cause of death among them.[1]

Atherosclerosis, or the hardening of the arteries, is caused by plaques that are formed when cholesterol, fat, calcium, and other toxic compounds come together. Heart failure, cardiac arrhythmias, cerebrovascular disease, and coronary artery disease might result from this procedure, depending on which vessels are impacted. While many distinct kinds of therapy been created to control CVDs, the majority of them have not proven effective in preventing or significantly

reducing the progression and prevalence of CVDs. New therapeutic approaches are beginning to emerge in light of the established negative effects of existing treatments. Given the significance of nanotechnology , particularly in treatment, it might be a innovative tool for treating and avoiding CVDs.[2]

Herbal remedies have been widely used for treating serious illnesses for a very long time. Furthermore, a large number of pharmacological compounds have plant origins. Natural chemicals are valuable for using in the search for novel therapeutic agents because of their wide chemical variety, low toxicity, therapeutic potential, and affordability.[3]

Natural yellow-colored alkaloid Berberine (BBR) is extracted from a plant named Coptis chinensis. It is a typical antibiotic used in Chinese medicine to treat dysentery and infectious diarrhea. Despite the fact that Chinese medicine has been using this plant for over 2500 years of history, though it has a potential to cure cardiovascular disease has grown within the past ten years. Berberine may protect preventing cardiac arrhythmia, diabetic, hyperlipidemia, high blood pressure, cardiac failure, and accumulation of plateletes, according to recent studies.[4]

To reduce the likelihood of pharmaceutical adverse effects and increase the efficiency of medication delivery, Nano formulation is a useful therapeutic strategy. Natural products and their derivatives that have been encapsulated offer special benefits that include decreased systemic unfavorable adverse reaction, improved health care, elevated medication bioavailability and solubility, longer exchange times, and limited build up in the intended organs. The distinct characteristics of the intended organs can guide the development of the precise kinds of nanostructures needed to treat illnesses.[5]

The field of nanotechnology studies atomic and molecular structures that range in size from 0.1 to 100 nm. In medicine, nanoparticle (NPs) are being used to improve imaging techniques in the initial phase of disease, to get into different sites (like the cerebral blood- brain barrier), and to send different therapeutic agents to target cells (like cancer cells that are selectively targeted without interfering via healthy tissue)[6]. Moreover, the replacement of damaged tissue regarding regenerative medicine makes substantial use of nanomaterials. Four primary uses of nanotechnologies in cardiovascular diseases (CVDs) include imaging of molecules, technology, regeneration of tissue, and targeted drug administration. In addition to discussing new developments in natural/herbal-based Nano formulations as effective drug delivery vehicles against CVDs.[7]

NANOFORMULATION AS A INNOVATIVE DRUG DELIVERY METHOD IN CARDIOVASCULAR ILLNESSES

Through the application of nanophases and nanostructures throughout various scientific fields, particularly in nanomedicine and medication delivery systems based on nanotechnology.[8]There are two primary medication delivery methods using various nanostructured materials nanocarrier system: organic nanocarriers (such as liposomes, polymeric nanogels, dendrimers, and a micelle and membrane nanocarriers) and inorganic nanoparticles (such as iron and gold tiny particles, silica mesoporous NPs, nanotubes made of carbon, and quantum dots).[9]

Drug targeting is the capacity of a drug molecule to accumulate at the sites of action, leading to a higher therapeutic index. As a delivery system based on nanoparticles, magnetic medication targeting is one of the many drug-targeted strategies system) is quite helpful.[10,11] For instance, by providing several amine groups, silanes create the perfect framework to adjust the surface functioning of the Fe3O4 nanoparticles for protein coupling. Surface coating with various polymers may be useful to improve the stability of NPs against oxidation.[12]

A wide range of therapeutic treatments are available for the treatment of heart problems in the context of CVDs after an episode of ischemia. Intracardiac catheterization or direct intramyocardial injection are frequent methods of delivering medications to the myocardium with greater assurance.[13] Even while intramyocardial injection has many

benefits, it is an intrusive procedure that can seriously harm the heart. However, embolization can be induced by intracoronary catheterization. Consequently, systemic intravenous medication injection is a better option. This procedure is less intrusive and offers the right environment for the cardiovascular system to receive enough medication circulation.[14]

In Atherosclerosis, Breakdown of macrophage rich atherosclerotic plaques in the coronary artery walls are the main cause of the sudden onset of acute cardiovascular syndromes in atherosclerosis. In general, focused therapy approaches may reduce the harmful effects of dosage on distant organs and suppress the activities of macrophages. For example, the most popular cholesterol-lowering medication, statins, can now be delivered efficiently in receptor-specific targeted vesicles, increasing the potential for high dose therapy in vulnerable plaques that selectively suppresses highly active macrophages.[15]

A sudden infraction of the heart, Due to cardiomyocytes' limited potential for regeneration and their sporadic aptitude for self-healing, therapy for acute myocardial infarction typically results in irreversible heart damage. Therefore, stem cell treatment is a helpful method for treating the target area of donated stem cells can only hold less than 10% of them due to cardiovascular diseases.[16] Super paramagnetic NPs made of iron oxide contain attracted increased interest as a solution to these problems. These NPs are applicable to the stem cell orientation and proliferation tracking.[17]

In Thrombosis, Systemic fibrinolytic therapy for thrombosis, which involves intravenously administering tissue plasminogen activator (tPA) to recanalisize occluded arteries, has been demonstrated to have numerous adverse effects in addition to limited efficacy. The medication’s accumulating within the thrombous area was enhanced by the use of magnetic nanoparticles for tPA orientation in the rat model target site. According to a different study, NPs were operationalized using the irreversible and specific thrombin inhibitor PAACK, enhanced PPACK's antithrombotic action and improved circulation time in an animal model.[18]

In congestive heart failure, A deadly cardiovascular condition that causes congestive heart failure is characterized by tissue death and decreased cardiac muscular function. It is routine practice to enhance myocardial contractility & cardiac function with inotropic medications like milrinone. This offers a novel approach to the sustained release profile and long term delivery of hemodynamically stable medications with minimal adverse effects. Additionally, it demonstrate the viability and efficiency of formulations based on nanoparticle in cardiovascular treatment.[19] For the purpose of delivering MRN targetedly, a unique nanoparticle formulation has been created. The AT1-HAS-MRN-NPs were created by surface modifying the HAS to create AT1-HSA. This innovative nanoparticle formulation has the potential to be employed in various cardiovascular conditions in addition to heart failure as a powerful, secure, and non-toxic treatment.[20]

MEDICINAL PLANTS AND PYTOCHEMICALS IN CARDIOVASCULAR DISEASE

A medication made from plant parts or the entire plant and prepared in a raw or refined form to cure or prevent illness is known as a medicinal plant. Primary or secondary metabolism produces substances known as phytochemicals, or natural products derived from plants. Primary or secondary metabolites found in plants are a good source for pharmacological research since they typically contain biological activity.[21] Table 1 lists several different kinds of therapeutic herbs that are used as alternative medicines for the treatment of CVDs. As an illustration, it was recently demonstrated that panax notoginsenoside’s saponin ingredients suchas ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rg3, and notoginsenoside R1, can prevent ischemia brain damage, expand peripheral arteries, shield against ischemic myocardial cells, and inhibit thrombosis.[22] Additionally, some phytochemicals, includingtilianin, cyclovirobuxine D, Berberine, curcumin, naringenin,and withanolides, have been shown to have

cardioprotective properties. QUE, myricitrin, baicalin, resveratrol, and allicin were reported in a number of investigations.[23-30] Berberine is a rhizome coptidis has a natural existing isoquinoline alkaloid, which is frequentlynutilized in Chinese traditional medicine fir its anti inflammatory and antibacterial effects. A growing body of research has shown promise in identifying multiple berberine's physiological and biological targets, suggesting that it may be used as s different kind of treatment for vascular illnesses.[31] Also it has been reported that, Plants high in berberine contain a variety of pharmacological and therapeutic properties, including immunomodulatory and antioxidant activities, as well as protective properties on the heart, liver, kidneys, relaxation of endothelium, regulator of glucose metabolism, atherosclerosis.[32] In addition to improving insulin resistance and lowering body weight, berberine's cardiovascular effects seem to be mediated through the AMPK cascade, the primary pathway linked to cardiovascular and metabolic disorders. As such, berberine is a promising addition to the toolkit for treatments of cardiac failure, metabolism syndrome and diabetes type 2.[33]

Table I: Phytochemical components of medicinal plants are used to treat cardiovascular diseases.

Botanical name	Family	Chemical compound	Actions	Reference
Nerium oleander	Apocynacea	gitoxigenin, digitoxigenin, nerium F, nerium D, neriodin, karabin, oleandrose, neriodorein, uzarigenin, oleanolic acid, tannic acid.	Antioxidants, Cardioprotective agent	[58]
The Sesbania grandiflora	Fabaceaea	Riboflavin, AA, minerals, vitamins A,C	Antimicrobial,Cardioprotective activitiy, anti-inflammatory	[59]
Tinospora cardiofolia	Tinospora	Berberine, columbin, gilosterol, tinosporol, giloinin, sesquiterpenoids, diterpenoid lactones, chasmanthin	Cardioprotective activit, antioxidant	[60, 61]
Ginkgo biloba	Genkgoaceae	Superoxide dismutase based on iron, flavonol, flavone glycosides, ascorbic acid, sequiterpenes, catechin, diterpen lactones, carotenoids, myricetin, quercetin, and ginkgolides	Activities that reduce stress, ageing, cytotoxic, hepatoprotective, anticoagulant, antidepressant, improve memory, reduce inflammation, and fight bacteria	[62, 63]
Zingiber officinale	zingiberaceae	10-gingerol, 8-ginegerol, 6-shogaol, 6-gingerol	Heart diseases, antimicrobial and Cardioprotective impacts against stroke	[64]
Prunus spp.	Rosaceace	Phenols	Antimicrobial activities, anticancer, antioxidant activities, and cardioprotective	[65]
Paeonia emodi	Paeoniaceae	Carbohydrates, phenolics, tannins, terprnoids	Antimicrobial, anti inflammatory, cardioprotective, antioxidant activities	[66]
Syzgium Cumini	Myrtaceaea	Flavonoid, aromatic compound and tannins	Anti inflammatory, antioxidant and cardioprotective	[67]
The Terminalia arjuna	Combretaceaea	polyphenols, arjuneti, flavonoids, freidelin,	Antioxidants and cardioprotective agent	[68,69]
Dracocephalum Moldavica	Labiataea	Tilianin, luteolin	Cardioprotective agent	[70]
Panax Notoginsenoside	Araliaceaea	Ginsenoside Rg1, Ginsenoside Rg3	Cardioprotective agent and anti-inflammatory	[71]

FORMULATION OF NANOTECHNOLOGIES IN THE TREATMENT OF CARDIOVASCULAR DISEASE

Despite berberine's diverse pharmacological actions, its low oral bioavailability and poor solubility create efficient Berberine distribution methods in order to address the aforementioned issues. As will be covered below, Berberine is currently developed and tested in numerous innovative ways for medication delivery.

LIPOSOMES

Liposomes, which range in size from 50-200 nm, produce phospholipid bilayer structures with natural phospholipids like cholesterol encasing aqueous cores. Because liposomes are both hydrophobic and hydrophilic, they can be utilized as efficient drug delivery vehicles.[34] Ploy (ethylene glycol) (PEG) might be added to the liposome membrane to give its transporter "shealth" like qualities. The shealth liposomes exhibit a longer half life in circulation, less absorption, and less liver or phagocyte clearance. Moreover, specific regions of the liposomal surface can be targeted by attaching antibodies or other targeting moieties to it.[35]Liposomes have the possibility to be used in the treatment of intermittent claudication and peripheral artery disease in cardiovascular therapy.[36] Phase III clinical trials are now being conducted on the liposomal drug delivery of prostaglandin E-1 (PEG-1), which is marketed under the trade name Liprostin. Numerous pharmacological characteristics of PEG-1 include vasodilation, anti inflammatory effects and inhibition of leukocyte adhesion or platelet aggregation. Liposomes are intended to specifically treat thrombus. Thrombous, a blood artery blockage, is linked to stroke and myocardial infraction.[37]

DENDRIMES

Dendrimers are branching units that are symmetrically oriented and around a tiny molecule or polymer core. According to reports, the studies used G4 to administer Berberine. PAMAM (polyamidoamine) by encapsulation and conjugation. Conjugation technique showed higher drug loading (37.49%) than encapsulation (29.9%). Conjugation and encapsulation showed nearly 98% and 72% discharge in water, respectively, during a 24-hour period in PBS 7.4. In contrast, these same percentages of release were seen in PBS 7.4. An albino rat model was used to do an in vivo pharmacokinetic profile.[38] The results showed that berberine's half-life (t1/2) and AUC were remarkable, with better plasma level time. As a result, conjugation-based distribution of Berberine utilizing PAMAM Dendrimers was found to be more effective than encapsulation-based Dendrimers.[39]

MICELLE SYSTEM

To improve berberine's hypoglycemic efficacy and oral bioavailability, a lyophilized anhydrous reverse micelle (ARM) administration method including amorphous Berberine was created using soya bean phosphatidylcholine. In type 1 diabetes produced by streptozotoc in mice, the hypoglycemic impact of Berberine injection (100 mg/kg and 2.5 mg/kg) and gavaged Berberine-ARMs was compared.[40] In contrast to injectable solutions, Following drug administration, Berberine loaded anhydrous reverse micelle showed a 57% drop in blood glucose level (BGL) in the first four hours and sustained for the complete twelve hours. A comparable set of mice was used for an in vivo pharmacokinetic research, along with an oral Berberine solution (100 mg/kg).It was demonstrated that Berberine-ARMs had improved intestinal absorption, leading to higher bioavailability.[41]

POLYMERIC NANOPARTICLES

Berberine polymer- lipid combination of tiny particles (BBR-SPCNP), composed of soybean phosphatidylcholine multifaceated were produced via solvent evaporation. The goal of this delivery method was to not only increase berberine's oral effectiveness but also foster affinity for biodegradable polymers for increased drug loading capacity and regulated medication release. Approximately 90% drug loading was attained, which was significantly higher than the ~37% drug loading that Berberine-loaded polymer nanoparticles (NPs/BBR) could obtain.[42]

The primary issues with polymeric materials employed in drug delivery are their biocompatibility and biodegradability, despite the fact that many of them have been used. Concerns regarding polymeric systems may also grow due to the available hazardous monomer accumulation, low drug absorption capacity, scalability difficulties, and toxicology information.[43]

METHOD OF PREPARATION OF NANOPARTICLES

SOLVENT EVAPORATION METHOD: Solvent evaporation was the initial method used to produce polymeric NPs from a polymer.This method requires the preparation of an oil-in-water (o/w) emulsion before it can be used to creat nanospheres. First, the polmer dissolved in a polar organic solvent and the active component immersed or distributed throughout comprises the organic phase. Chloroform and dichloromethane have been employed extensively, but more frequently in the past. Owing to its toxicity, ethyl acetate has taken their place because it has a superior toxicological profile and is therefore more appropriate for use in biological applications.[44] It has also been common practice to prepare an aqueous solution containing a surfactant (like PVA or polyvinyl acetate). After emulsifying the aqueous phase of the organic solution with a surfactant, high-speed homogenization is usually used to process it or ultra-sonication, which results in a Nano droplet dispersion. An emulsion's continuous phase is where the polymer solution evaporates and diffuses, creating a suspension of nanoparticles. When using more polar solvents, the solvent is continuously stirred magnetically at room temperature to evaporate it; otherwise, the solvent evaporates slowly under reduced pressure, as is the case when employing dichloromethane and chloroform, for example. Following the evaporation of the solvent, For long term storage the cleaned and solidified nanoparticles can be freeze dried after being collected and centrifuged.[45]

EMULSIFICATION/SOLVENT DIFFUSION: With this technique, an o/w emulsion is created between an aqueous solution containing a surfactant and a partly water-miscible fluid containing a polymer and medication. The internal phase of the emulsipon is composed of an organic solvent that is slightly hydro miscile, such as benzyl alcohol,or to ensure that both phases first reach thermodynamic equilibrium at ambient temperature , ethyl acetate is first saturated with water. Colloidal particles are created as a result of the ensuing large-scale dilution, which promotes solvent migration in to the exterior phase from the scattered droplets.[46] This process is typically used to create Nano spheres, but it is also possible to create Nano capsules by adding a tiny quantity of oil such as triglycerides, which are found in the carbon chains C6, C8, C10, and C12 to the organic phase. In conclusion, contingent upon the organic solvent's boiling point, this final phase can be removed through filtration or evaporation. Ultimately, it is possible to obtain NPs with sizes ranging from 80 to 900 nm. This method is frequently employed to create polymeric NPs, despite the requirement to remove a significant amount of the aqueous phase form the colloidal dispersion and the potential for the hydrophilic medication to diffuse into the aqueous phase .[47]

SALTING OUT METHOD: It is among the frequently employed techniques for nanoparticle preparation. Using magnetic stirring, an acetone solution of the polymer and a saturated aqueous solution of polyvinyl alcohol (PVA) are combined to form a o/w emulsion. The polymer forms precipitates when sufficient water is added to the external phase to allow the internal phase into the aqueous phase.[48,49]

POLMERIZATION METHOD: This method entails incorporating the drug after monomers are polymerized in an aqueous solution. Either by sticking to the nanoparticles or ny dissolving in the polymerization solvent. The solution of nanoparticles is refined and subsequently reconstituted in a medium devoid of isotonic surfactants, following the removal of various stabilizers and surfactants utilized in the polymerization process using ultra-centrifugation. This method has been published for the synthesis of polybutyl cyanoacrylate or poly (alkylcyano acrylate) nanoparticles. The concentration of the stabilizers and surfactants utilized influences the formation of Nano capsules and the size of their particles.[50]

COACERVATION OR IONGELATION METHOD: The synthesis of nanoparticles from hydrophilic biodegradable polymers, such as gelatin, chitosan and sodium alginate, has been extensively studied. A technique created by Calvo and associates for ionic gelation to produce hydrophilic chitosan nanoparticles /39, 40 Two aqueous phases make up the method: The polymer chitosan is present in one phase and sodium tripolyphosphate, or a polyanion is present in the other. Through the collision of the positively charged amino group of chitosan with the negatively charged tri polyphosphate, this method produces coacervates with in the manometer size range. Coacervates are formed when two aqueous phases interact electrostatically, and ionic gelation, under room temperature ionic interaction circumstances, causes a liquid to turn into a gel.[51,52]

EVALUATION OF NANOPARTICLES

Particle size analysis: The measurements of the nanoparticles were made using the scanning electron microscope, diameters of nanoparticle, which ranged from 350 nm to 600 nm. The polymer load affects the size of the particles.[53,54]

Scanning electron microscopy (SEM): The surface morphology and particle shape of the nanoparticles have been examined by scanning electron microscopy. Following lyophilization and thorough drying, samples were positioned using adhesive tapes on aluminum stubs, coated with gold using a sputter coater and morphological analysis was performed at 20kv acceleration voltage.[54]

Differential scanning calorimetry (DSC): To ascertain the physical conditions of the native medication within the nanoparticles, the DSC analysis 9DSC-60) was employed. The natural medication, polymer and particles, each weighing about 2 mg, were added individually to separate sealed standard aluminum pans and heated in a nitrogen environment at a rate of 10ºc per minute between 25ºc and 300ºc.[53]

Drug entrapment efficiency percentage: The suspensions of prepared nanoparticles underwent centrifugation for 30 minutes at 2000 rpm. After gathering the supernatant, the particles underwent a water wash before undergoing one more centrifugation cycle. The ultra-violet-visible spectrophotometer was used to measure the quantity of complimentary drug found in the supernatant.[55]

Drug Entrapment (%) = Amount of drug added-Amount of free drug/Amount of drug added × 100

Determination of Zeta potential: The zeta potential of the drug-loaded chitosan nanoparticles was determined by measuring the electrophoretic mobility in a micro electrophoresis flow cell using zetasizer (Malvern instruments). Three measurements were made of each sample in water at 25 °C.[56,57]

FUTURE PROSPECTS OF BERBERINE NANOPARTICLE

Berberine nanoparticle have shown promising potential for cardiovascular disease treatment. They can enhance the therapeutic effects of Berberine by improving its bioavailability and targeting specific cells in heart. It is considered as existing area of research.[19]

Their small size allows for better absorption and distribution in the body, leading to enhanced therapeutic effects. These nanoparticles can specifically target the cells involved in cardiovascular disease, Such as endothelial and cardiac muscle cells, increasing their efficacy.[73]

The recent research has demonstrated that Berberine nanoparticle can decrease inflammation, oxidative stress, and cholesterol levels in heart. They also have the potential to regulate blood pressure and improve heart function. Thereby Berberine nanoparticle also found to inhibit the formation of plaque in blood vessels, which helps to prevent atherosclerosis.[58]

The use of nanoparticles also allows for controlled and sustained release of Berberine, ensuring a longer therapeutic effect. They have a targeted and prolonged delivery system which enhance the efficacy of Berberine in treating cardiovascular disease.[73]

Overall, the future of Berberine nanoparticle in the therapy of cardiovascular disease have feasible to revolutionize in the field and provide new more effective treatment.[74]

CONCLUSION:

This review indicates that there is a promise for using nanotechnology to treat cardiovascular disease. It is a given that that nanotechnology has the potential to enhance patient health and wellness, and that any advancements in existing treatments will have a positive world-wide influence on patient outcomes.

According to the presentation, the effectiveness of a plant extract's Nano formulation and its bioactive phytochemicals is noticeably more than that of a standard formulation. The chemical properties and functions of nanoparticles are influenced by their synthesis techniques and formulation type. Numerous nanoformulations have been used and studied to date to combat cardiovascular disease in both in vitro and invivo settings. Additionally, there is a need to use nanoparticles in cardiovascular therapy clinical trials more quickely, effectively and affordbly

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