Status of Herbal Drugs in Cardiovascular Research: A Review

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Abstract

Globally, cardiovascular diseases (CVD) constitute a leading cause of mortality. Heart disease in India occurs 10 to 15 years earlier than in the west. One fifth of the deaths in India are from coronary heart disease (CHD). The global burden of disease due to cardiovascular diseases (CVDs) is escalating, principally due to a sharp rise in the developing countries which are experiencing rapid health transition. More than 2000 plants have been listed in the Traditional (Herbal/Alternative) systems of medicine and some of these are providing comprehensive relief to the people suffering from cardio-vascular diseases, specially "hyperlipidemia" and "ischemic heart disease". WHO reports indicate that around eighty percent of the global population still relies on botanical drugs and several herbal medicines have advanced to clinical use in modern times. This review work explains chemical and pharmacological status of various cardioprotective plants including phytoconstituents responsible for cardioprotection, pharmacological screening model and mechanism involved in cardioprotection.

Keywords: Cardiovascular diseases, antioxidant, cardioprotective, phytoconstituents.

1. INTRODUCTION

There is little doubt that Traditional Medicines have been utilized since antiquity in the health care. However, with the advent of the pharmaceutical industry early in this century, the popularity of traditional/herbal medicine declined, in spite of the fact that twenty five percent of all prescription drugs still contain ingredients isolated from plants. The resources now do exist which can help and assist for greater understanding of the ways in which herbs can facilitate health and restore balance in disease[1].

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Herbal medicine is increasingly gaining greater acceptance from the public and medical profession due to greater advances in understanding of the mechanisms by which herbs positively influence health and quality of life[2]**.** A major portion of the global population in developing countries still relies on botanical drugs to meet its health needs. The attention paid by health authorities to the use of herbal medicines has increased considerably, both because they are often the only medicine available in less developed areas and because they are becoming a popular alternative treatment in more developed areas. Thus herbal medicines have been given a valuable status and readily available products for primary health care, and WHO has endorsed their safe and effective use[3].

Cardiovascular diseases (CVDs) are the most prevalent cause of death and disability worldwide. CVD a group of disorders of the heart and the vasculature includes high blood pressure coronary heart disease, congestive heart failure, stroke and congenital heart defects. The world health organization (WHO) estimates that 17 million people die of cardiovascular disease annually. WHO predicts that deaths due to circulatory system diseases are projected to double by 2015[4]. The synthetic drugs that constitute the current pharmacological armamentarium are themselves effective in managing the condition but not without setbacks. These hunches have accelerated the need for natural products with better efficacy and fewer side effects [5].

More than 2000 plants have been listed in the Traditional (Herbal/Alternative) systems of medicine and some of these are providing comprehensive relief to the people suffering from cardio-vascular diseases, specially "hyperlipidemia" and "ischemic heart disease". WHO reports indicate that around eighty percent of the global population still relies on botanical drugs and several herbal medicines have advanced to clinical use in modern times[6]. Although, some traditional Chinese Medicines have been used in mainland, Hong Kong, Taiwan of China in clinics and other Chinese communities worldwide for centuries[7]. The use of Western medicinal drugs for the treatment of hypertension, congestive heart failure and post myocardial infarction are widely

accepted. For cardiovascular diseases, herbal treatments have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency and arrhythmia[8].

Doubts have been raised for the use of herbal drugs on the reasons that (i) herbs of different origin are often known by the same popular name, (ii) plants growing in different climatic soil and seasonal conditions do not have identical chemical constituents or therapeutic effect, (iii) process of collection (fresh, shade or sun dried) extraction, processing and storage of herbal medicines cause variation in potency and safety, (iv) no specific standards for herbal medicines have been prescribed and (v) non availability of these herbal medicines in suitable dosage form created difficulty in administration. These shortcomings have delayed the integration of some of the well recognised Ayurvedic or Unani recipes in the modern system of medicine[9].

2. HERBAL COMPOUNDS AS ANTIOXIDANTS:

Reactive oxygen species (ROS) including superoxide radicals, hydroxyl radicals, singlet oxygen and hydrogen peroxide are often generated as byproducts of biological reaction or from exogenous factors[10]. *In vivo*, some of these ROS play an important role in cell metabolism including energy production, phagocytosis and intercellular signalling[11]. However, these ROS produced by sunlight, ultraviolet light, ionizing radiation, chemical reactions and metabolic processes have a wide variety of pathological effects such as DNA damage, carcinogenesis and various degenerative disorders such as cardiovascular diseases, aging and neuro-degenerative diseases[12-14].

Recent studies have shown that a number of plant products including polyphenols, terpenes and various plant extracts exerted an antioxidant action[15-18]. There is also a considerable amount of evidence revealing an association between individuals who have a diet rich in fresh fruits and vegetables and the decreased risk of cardiovascular diseases and certain forms of cancer[19,20]. In recent decades, substantial interest has been focused on antioxidant therapeutic strategies for cardiovascular disease. It is emparative to emphasize effective preventive strategies for the cardiovascular disease epidemic. In

years past, vegetable, fruit and antioxidant-rich Mediterranean diets have been highlighted, since a number of epidemiological studies have shown a strong inverse relationship between cardiovascular disease and vegetable and fruit rich diets [21]. The World Health Organization recommends 500g of fresh fruits and vegetables per day[22]. Antioxidant micronutrients have attracted special attention, particularly vitamin E, vitamin C, beta carotene and other carotenoids, such as lutin, zeaxanthin and lycopene, which have the greatest singlet oxygen quenching properties[23]. More recently, there has been increased interest in putative dietary antioxidants like bioflavonoids, flavonals like quercetin or special phenol derivaties in red wine and oxygen sensitive B complexes, which are involved in the metabolism of homocysteine and L-arginine[24,25]. Flavonoids are effective antioxidants in plants as well as in animals[26] . Flavonoids are identified as potential risk reducing components in the diet for cardiovascular disease, various cancers, neurodegenerative diseases, etc[27]. For example, quercetin-3-*O*-glucoside, a flavonoid compound ubiquitous in fruits, has shown protective effect on human neuroblastoma cells (SH-SY5Y) against oxidative stress by a membrane injury recovery mechanism that is involved in up-regulation of genes involved in lipid and cholesterol synthesis[28].

3. HERBAL COMPOUNDS AS ACE INHIBITORS:

Hypertension is the most common cardiovascular disease and a major public health problem in both developed and developing countries[29]. A large number of population surveys from different parts of the globe have consistently demonstrated hypertension to be a ubiquitous disease encompassing all ethnic groups and geographic region[30,31].High blood pressure occurs when the body's smaller blood vessels (known as the arterioles) narrow, thereby causing the blood to exert excessive pressure against the vessel walls. The heart works harder to maintain higher blood pressure. Although the body can tolerate increased blood pressure for months and even years, eventually they enlarge and got damaged. Hypertension has been aptly called a silent killer, because it usually produces no noticeable symptoms. Hypertension is referred to as essential, or primary, when

the physical is unable to identify a specific cause. This is by far the most common type of high blood pressure, occurring in up to 95% of patients[32]. Herbal treatments are usually necessary. A single plant root can often control mild to moderate hypertension. More severe hypertension often requires a combination of two or more plant combination. In addition to helping lower blood pressure, herbal medicine provides health benefits[33].

Angiotensin converting enzyme (ACE) is a key component in the renin angiotensin aldosterone system (RAAS) which regulates blood pressure. As the over expression of RAAS is associated with vascular hypertension, ACE inhibition has become a major target control for hypertension. The research on potential ACE inhibitors is expanding broadly and most are focused on natural product derivatives such as peptides, polyphenolics, and terpenes. Plant polyphenolics are antioxidant molecules with various beneficial pharmacological properties[34]. Some terpenoids and polyphenolic compounds including flavonoids, hydrolysable tannins, xanthones, procyanidins, caffeolyquinic acid derivatives are found to be effective as natural ACE inhibitors[35,36]. Most studies have showed that plant extracts rich in phytochemicals found to be effective in ACE inhibition. However, identification of compounds specifically inhibit ACE is lacking in most of these investigations. Plant-derived peptides have been identified from different sources including soybean, flaxseed, sunflower, rice, and corn. Anthocyanins have shown ACE inhibition *in vitro*. Delphinidin-3-*O*-sambubiosides and cyanidin-3-*O*-sambubiosides isolated from Hibiscus (*Hibiscus sabdariffa*) extracts had inhibited ACE in a dose dependant manner[37]. Similarly, cyanidin-3-*O*-β-glucoside isolated from rose species (*Rosa damascene*) inhibited ACE *in vitro*. However, other flavonols isolated from rose extract were not effective ACE inhibitors when compared to cyanidin-3-*O*-β-glucoside[38]. Bilberry (*Vaccinium myrtillus*) extracts rich in major anthocyanins i.e. cyanidin, delphinidin and malvidin, were investigated on their effect on ACE in a human umbilical vein endothelial cell (HUVEC) culture model and the ACE activity had been significantly reduced after incubation of cells with bilberry extracts [39] .The four major catechins, (–

)-epicatechin, (–)-epigallocatechin, (–)-epicatechingallate and (–)-epigallocatechingallate, isolated from tea had also shown a dose dependant ACE inhibition in a HUVEC culture model[40]. Pycnogenol, a procyanidin oligomer, isolated from French maritime pine (*Pinus maritime*) had also reported as an effective mediator for blood pressure regulation possibly by ACE inhibition[41]. These studies prove that among flavonoids, flavanols and procyanidins could also act as potent inhibitors of ACE *in vitro*.

4. HERBAL COMPOUNDS AS NADPH OXIDASE INHIBITORS :

Most estimates suggest that the majority of intracellular ROS production is derived from the mitochondria. The production of mitochondrial superoxide radicals occurs primarily through an enzyme NADPH oxidases. NADPH oxidases are a family of multi subunit enzyme complexes that are unique in being the only enzymes that have been identified with the primary function of generating superoxide and/or hydrogen peroxide. The primary catalytic function of the NADPH oxidase family of enzymes is the generation of ROS. The ROS generated by NADPH oxidases have crucial roles in various physiological processes. Recently it has been emerged that excessive ROS production by an overactive NADPH oxidase system in vessel wall may set in motion a vicious cycle of radical and non-radical oxidant generation in various cellular compartments, which disrupts redox circuits[42,43]. The naturally occurring methoxyphenol apocynin has been found to inhibit NADPH oxidase upon activation by peroxidases (e.g. soybean peroxidase, myeloperoxidase) or ROS under mild reaction conditions. Upon peroxidase-catalyzed activation, the apocynin oxidation products act to block the assembly and activation of NADPH oxidase. Although the mechanism of inhibition of NADPH oxidase remains largely unknown, apocynin's high effectiveness and low toxicity makes it a promising lead compound in the development of new therapeutic agents for cardiovascular diseases[44].

5. HERBAL COMPOUNDS AS PLATELET AGGREGATION INHIBITOR:

Platelet receptors on the surface of the platelets determine the reactivity of platelets and have a wide range of

agonists and adhesive proteins[45]. Current antiplatelet therapies target key pathways of platelet activation, including surface receptors and signalling molecules. Aspirin has been the foundation of antiplatelet therapy for over 50 years, and it inhibits platelets by irreversibly acetylating Ser529 of cyclooxygenase 1 (COX1), thereby inhibiting thromboxane A2 formation by the platelets. Aspirin has been shown to reduce vascular death in high-risk patients by 15% and nonfatal vascular events by 30%, as evidenced by meta-analysis of over 100 randomized trials[46,47]. Several medicinal plants have direct or indirect antiplatelet effects, many through inhibition of COX1 or 2. Likewise, a variety of fruit extracts have been tested *in vitro* for their antiplatelet property, and tomatoes have been found to have a very high activity[48]. It was showed that tomato extract inhibited both ADP- and collagen induced aggregation by up to 70%. Various fruit juices have also been tested, and some flavonoids have been established as inhibitors of collagen-induced platelet activity[49,50]. The effect of flavonoids is well established, and for coffee, it was showed that the caffeine is not the inhibitor [51] but rather the phenolics that was also found inside the platelets. Many of the effects observed are often due to synergistic effects, which are also seen on tomato and grape juice, and the effect can be expected to be lower for the individual compounds [48-51].

Garlic preparations are taken by many patients because of their anti-lipid and anti-platelet effects, significant factors in the prevention of thrombus formation[52-54]. The allicin derivative of garlic root has been shown to enhance fibrinolytic activity and inhibit platelet aggregation in patients with coronary artery disease[55-57], either via a dose-dependent alteration in the production of arachidonic acid metabolites (i.e. inhibition of thromboxane formation in platelets[56,58,59] or by altering physiochemical properties (i.e. the ADP-receptor) of the platelet membrane[60-62]. Other herbs may also affect platelet function through inhibition of prostaglandin metabolism. Ginger, used by pregnant women for the relief of nausea and vomiting[63,64], reduces the production of PG-endoperoxides and thromboxane through either inhibition of platelet cyclooxygenase (COX) [65] or as a result of the anti-oxidant components in

the herb which suppress the lipid peroxide essential for COX activity [66,67]. Feverfew, an herb used to treat migraine headaches[68-70], suppresses upto 88% of prostaglandin production without inhibiting COX[71-75], while clove – a common kitchen spice and important source of dietary antioxidants[76], contains two antiplatelet components (eugenol and acetyl eugenol) which inhibit platelet thromboxane formation and increase formation of 12-HPETE, both of which are more potent than aspirin in their antiplatelet effects[77]. Bromelain, a derivative of pineapple with immuno-modulatory effects[78], also inhibits platelet prostaglandin synthesis[79], while the coumarin-containing herb licorice (with the 3-arylcoumarin derivative GU-7[80] inhibits COX, lip-oxygenase and peroxidase activity in platelets [81].

Some herbs affect platelet function through other mechanisms. In addition to its anticoagulant effect, the Chinese herb Danshen inhibits platelet aggregation and release via increasing intracellular cyclic AMP[82]. Ginseng, a popular herb comprising 15–20% of the total annual sales of botanical products in the United States[83] (whose real benefits are still controversial[84], inhibits platelet aggregation induced by thrombin or collagen in the rat model[85]. Ginkgo biloba, use by Chinese doctors for centuries for the treatment of "chest complaints", has been shown in clinical studies to be superior to placebo for intermittent claudication[86] and (questionably) beneficial for dementia as well[87,88]. The increased risk for bleeding in patients using this herb is thought to be due to a dose-dependent inhibition of PAF-induced platelet aggregatio[89]. Red pepper (capsaicin), an herb used to alleviate diabetic neuropathy[90], inhibits platelet aggregation and release [91], as well enhancing fibrinolytic activity[92].

6. HERBAL DRUGS LOWERING CHOLESTEROL:

Hyperlipidemia (Elevated cholesterol or triglyceride) is a major cause of atherosclerosis and atherosclerosis associated conditions such as coronary heart disease, ischemic cerebrovascular disease and peripheral vascular disease. The lipid metabolism is regulated in many different ways. Enzymes are major regulators of lipid metabolism[93]. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is one of the enzymes involved in cholesterol biosynthesis[94]. There are several

antihyperlipidemic drugs available in market like statins, fibrates, niacin etc. Various herbal drugs are also potent antihyperlipidemic but their mechanism of action is still unclear. Some of these drugs are *Andrographis paniculata, Anthocephalus indicus, Ocimum sanctum, Picrorrhiza kurroa, Plumbago zeylanica*, *Terminalia arjuna* [95-100] .They might be acting through inhibition of HMGCoA Reductase.

Polyphenols are common constituents of botanical extracts available in over-the-counter nutraceutical preparations and are found in different fruits and vegetables, olive oil, and beverages like red wine and tea. Consumption of polyphenols in the diet has been shown to reduce the likelihood of morbidity and mortality from coronary artery disease[101]. One way in which polyphenols are thought to act is through the inhibition of lipid peroxidation of low-density lipoprotein (LDL) [102]. Dietary supplements rich in polyphenols, such as black and green tea[103], olive oil[104], red wine[105], and licorice root extract[106], are associated with an increased resistance of plasma LDL oxidation. Indeed, consumption of tea extract, red wine or licorice extract by hyper-cholesterolemic apolipoprotein E (apoE)-deficient mice caused a significant reduction in atherosclerosis[106-108].

Tsi *et al* studied the antihyperlipidaemic property of aqueous extract of celery, *Apium graveolans* Linn. (*Badi Ajmod*) in rats. A significant reduction was reported by them in the serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) concentrations in rats[109] .The lipid lowering and antioxidant potential of ethanolic extract of adraka or ginger, *Zingiber officinale* Rosc. was evaluated in streptozotocin (STZ)-induced diabetes in rats by Bhandari *et al*. Ethanolic extract of ginger (200 mg/kg) fed orally for 20 days produced significant antihyperglycaemic effect ($P < 0.01$) in diabetic rats. Further, the extract treatment also lowered serum total cholesterol, triglycerides and increased the HDL cholesterol levels when compared with pathogenic diabetic rats[110]. The alcoholic extract of *Achyranthes aspera* Linn**.**, at 100 mg/ kg dose lowered serum cholesterol (TC), phospholipid (PL), triglyceride (TG) and total lipids (TL) levels by 60, 51, 33 and 53%, respectively in triton induced

hyperlipidaemic rats. The chronic administration of this drug at the same doses to normal rats for 30 days, lowered serum TC, PL, TG and TL by 56, 62, 68 and 67%, respectively followed by significant reduction in the levels of hepatic lipids[111] . The lipid lowering activity (LLA) of *Phyllanthus niruri* Hook. f. Has been studied by Khanna and others in triton and cholesterol fed hyperlipemic rats. Serum lipids were lowered by *P. niruri* extract orally fed (250 mg/kg b.w.) to the triton WR-1339 induced hyperlipemic rats. Chronic feeding of this drug (100 mg/kg b.w.) in animals simultaneously fed with cholesterol (25 mg/kg b.w.) for 30 days caused lowering in the lipids and apoprotein levels of VLDL and LDL in experimental animals[112] .The effects of the administration of 50 mg of guggulipid of *Commiphora mukul* (Hook. ex Stocks) Engl. Or placebo capsules twice daily for 24 weeks were compared by Singh and others as adjuncts to a fruit- and vegetable-enriched prudent diet in the management of 61 patients with hypercholesterolaemia (31 in the guggulipid group and 30 in the placebo group) in a randomized, double-blind fashion. Guggul lipid decreased the total cholesterol level by 11.7%, the LDL-cholesterol by 12.5%, triglycerides by 12.0%, and the total cholesterol/ HDL-cholesterol ratio by 11.1% from the post diet levels, whereas the levels were unchanged in the placebo group[113].

Some Herbal Cardioprotective Compounds: Table 1. Shows the various herbal Cardioprotetive compounds[114-144].

S. No.	Plant name	Chemical compound	Model (*In-vivo/In -vitro*)	Activity
1)	*Cnidium monnieri* (Umbelliferae)[114]	Osthol	Spontaneously hypertensive rat	Lowers blood pressure and cholesterol
2)	*Genista tinctoria* (Fabaceae)[115]	Genistein	Spontaneously hypertensive rat	Up regulates nitric oxide synthase and lowers blood pressure.
3)	Various plants[116]	Ursolic acid	Isolated perfused beating rabbit atria	Increase atrial natriuretic peptide secretion
4)	*Gingko biloba* (Gingkoaceae)[117]	Bilobalide	Neonatal rat cardiomyocyte	Anti-ischemic

5)	*Ficus racemosa* (Moraceae)[118]	Kaempferol	Aortic tissues of male wistar Kyoto rats.	ACE inhibition
6)	*Bacopa monnieri* (Scrophulariaceae)[119]	Bacosides A and B	Isoproterenol induced myocardial necrosis in rats	Antioxidant
7)	*Cinnamomum tamala* (Lauraceae)[120]	Cinnamaldehyde	High Cholesterol Diet Induced Hyperlipidemia	Antihyperlipidemic
8)	Grape (Vitaceae)[121] activity	Resveratrol	Rat aortic homogenates	Decreases NADH/NADPH activity
9)	*Commiphora mukul* (Burseraceae)[122]	Guggulsterone isomers	Isoproterenol induced myocardial necrosis in rats *(in vivo)*	Inhibit oxidative degradation of lipids in human low-density lipoprotein *in vivo*
10)	*Mangifera indica* (Anacardiaceae)[123]	Magniferin	Isoproterenol induced myocardial infarction in albino rats	Decrease lipid peroxide formation
11)	*Silybum marianum* (Compositae)[124]	Silymarin	Ischemia-reperfusion-induced myocardial infarction in albino rats	Protect the endogenous antioxidant enzymes, suppress the neutrophil infiltration during ischemia-reperfusion and limit the infarct size.
12)	*Daphne giraldii Nitsche* (Thymelaeaceae)[125]	Daphnetoxin, Gniditrin	-	Cholesterol lowering
13)	*Pinus maritime* (Pinaceae)[126]	Pycnogenol	Reduction of cardiovascular risk factors in subjects with type 2 diabetes	ACE inhibition
14)	*Green tea*[127]	Catechin ,epigallocatechin	Murine pulmonary thrombosis	Antithrombotic
15)	*Sophora Japonica* (Fabaceae)[128]	Rutin	Anaesthetized rats subjected to coronary artery ligation	Reduce the infarct size and prevents the loss of the 'R' wave

16)	Various fruits[129]	Quercetin 3-O-glycosides	Human neuroblastoma cells(SH-SY5Y)	Antioxidant
17)	*Hibiscus sabdariffa (Malvaceae)*[130]	Delphinidin-3-*O*-sambubiosides and cyanidin-3-*O*-sambubiosides	-	ACE Inhibition
18)	*Vaccinium myrtillus (Ericaceae)*[131]	Cyanidin, delphinidin and malvidin	Human umbilical vein endothelial cell (HUVEC) culture model	ACE Inhibition
19)	*Hydrocotyle asiatica* (Umbelliferae)[132]	Asiatocoside,madecassoside, madasiatic acid, cintella and fatty acid polyacetylene	Ischemia-reperfusion induced myocardial infarction in rats	Myocardial infarction
20)	*Ligustrum delavayanum* (Oleaceae)[133]	Iridoid glycosides, quercetin-3-o-β-D-glucodside, quercetin-triglycoside, luteolin-7-o-β-D-glucoside, kempferol-7-o-rhamnoside	Myocardial ischaemia–reperfusion injury in diabetic-hypercholesterolemia rats	Decrease cholesterol levels
21)	*Desmodium gangeticum* (Fabaceae)[134]	Protocatechuric acid, chlorogenic acid, gallic acid, rutin, quercetin,	Myocardial ischemia reperfusion injury in rat hearts	Antioxidant

		kaempferol, β-sitosterol, stigmasterol and lauric acid.		
22)	*Tinospora cordifolia* (Menispermaceae[135]	Berberine and columbin.	Ischemia reper-fusion induced myocardial infarction in rats.	Myocardial infarction
23)	*Crataeva nurvala* (Capparidaceae)[136]	Lupeol	Cyclophosphamide-induced hyperlipidaemic cardiomyopathy in rats.	In hyperlipidaemic cardiomyopathy
24)	*Sida rhomboidea* (Malvaceae)[137]	Cryptolepine, ephedrine, vasicine	Isoproterenol induced myocardial necrosis in rats	Myocardial necrosis
25)	*Eugenia uniflora* (Orchidaceae)[138]	Carotenoids, flavonoids	Rat thoracic aorta	Nitric oxide upregulation
26)	*Curcuma amada* (Zingiberaceae)[139]	Amadaldehyde	-	Platelet aggregation inhibitor
27)	*Allium sativum* (Liliaceae)[140]	Allicin	Rats fed with a high cholesterol diet	Reduces blood cholesterol, triglycerides levels and systolic blood pressure
28)	*Evodia rutaecarpa* (Rutaceae)[141-144]	Rutaecarpine	Guinea pig isolated right atria, presensitized guinea pig thoracic aorta challenged with antigen, human platelet-rich plasma, monocyte-like cell line THP-1 and promyelocytic leukemia cell line HL60.	Positive inotropic and chronotropic effects, inhibits vasoconstriction, inhibits platelet aggregation, anti-atherosclerosis

CONCLUSIONS:

It has been suggested that, for the future drug development, herbs may be an important source of new compounds which may have fewer side effects. The understanding of the precise pharmacological properties of herbals will definitely help the development of new drugs. The review summarizes the studies on the cardiovascular effects of various herbals, which provides extensive and strong evidence for the potential use of herbal drugs in the treatment of cardiovascular diseases.

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