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Review Article

CARDIOPROTECTIVE POTENTIAL OF PLANTS AND PLANT-DERIVED PRINCIPLES − A REVIEW

NIKITHA G, RAJENDRA SANDUR V*

Department of Pharmacology, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India. Email: drrajendra1972@gmail.com

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ABSTRACT

Cardiovascular diseases (CVDs) are a class of diseases involving heart or blood vessels. Coronary artery diseases include angina, myocardial infarction (MI), stroke, heart failure, hypertensive heart disease, cardiomyopathy, and arrhythmias. CVDs are the leading cause of death globally. Risk factors include high blood pressure, smoking, obesity, poor diet, blood cholesterol, and lack of exercise. It is approximated that 90% of CVDs is preventable. High blood pressure results in 13% of CVD deaths, whereas tobacco outcomes in 9%, diabetes and lack of exercise in around 6%, and obesity in 5%. Due to certain medications such as anticancer drugs like doxorubicin, adverse effects result in MI. Since ancient times, medicinal plants have been widely used in the treatment of diseases. This information may serve as a primer in identifying novel prophylactic as well as therapeutic studies of plant-derived principles. The parts of the plants such as seeds, leaves, flowers, roots, and bark contain these phytoconstituents which are obtained through different extraction processes. Phytoconstituents are broadly classified into alkaloids, saponins, polyphenols, essential oils, carotenoids, glycosides, omega fatty acids, and flavonoids. Each class is responsible for its own pharmacological effects. The underlying mechanism in which they exert the action is different. This review presents an overview of the MI and therapeutic strategies of plant-derived principles that are available to mitigate the effect of MI.

Keywords: Cardiovascular diseases, Myocardial infarction, Medicinal plants, Phytoconstituents, Alkaloids, Saponins, Sulfur-containing compounds, Carotenoids, Flavanoids, Essential oils, Polyphenols.

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INTRODUCTION

Medicinal plants, also called medicinal herbs, have been identified and used in ancient medicine practices since prehistoric times. Plants synthesize hundreds of chemical compounds for functions including defense against insects, fungi, diseases, and herbivorous mammals [1]. There are four major biochemical classes of phytoconstituents found in plants which include alkaloids, glycosides, polyphenols, and terpenes. Medicinal plants are widely used in underdeveloped societies, mainly because they are readily available and cheaper than the modern medicines. Cardiovascular disease (CVD), predominantly myocardial infarction (MI), is one of the leading causes of death worldwide [2]. Acute MI is the most important and serious consequence of coronary artery disease. It occurs when myocardial ischemia, decreased blood supply to heart, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal operating function and homeostasis [3]. MI is invariably followed by numerous pathophysiological and biochemical alterations including hyperlipidemia, thrombosis, lipid peroxidation (LPO), and free radicle damage, leading to qualitative and quantitative changes of myocardium [4]. Although clinical care is improvised, public awareness is raised, and health innovations are widely used, MI still remains the leading cause of death worldwide [5].

Secondary metabolites and their cardioprotective role

Secondary metabolites are organic compounds synthesized by plants which are not directly involved in the normal growth, development, or reproduction of the organism. One of the most important defining qualities of secondary metabolites is their specificity [6]. There are a number of plants containing various classes of phytoconstituents responsible for cardioprotective activity as summarized in Table 1.

Role of secondary metabolites in cardioprotection

Alkaloids

Alkaloids are a class of naturally occurring phytoconstituents that mostly contain basic nitrogen atoms. In addition to carbon, hydrogen, and nitrogen, alkaloids may also contain oxygen, sulfur and, more rarely, other elements such as chlorine, bromine, and phosphorus [7]. Alkaloids are synthesized by a large variety of organisms including bacteria, fungi, plants, and animals [8]. They can be obtained from the purification of the crude extracts of these organisms by acid–base extraction. Alkaloids have a wide range of pharmacological activities including antimalarial [9], anticancer [10], vasodilatory [11], antiarrhythmic [12], analgesic [13], antibacterial [14], and antidiabetic [15] activities.

Tinosporin

Tinospora cordifolia is an herbaceous vine of the family *Menispermaceae* which is indigenous to the tropical areas of India, Sri Lanka, and Myanmar. Also called Guduchi in Ayurvedic medicine, a variety of active components such as alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and the whole plant [16]. The alkaloids which are predominantly found in *T. cordifolia* include tinosporin (Table 2), berberine, and palmatine which are present in the stems. Dose-dependent reductions in infarct size and in serum and heart lipid peroxide levels were perceived significantly with prior treatment of the extract in ischemia-reperfusion (I/R)–induced MI in rats [17]. Physical parameters include gross examination of the heart and heart weight/body weight ratio and in biochemical estimation, the various cardiac enzymes such as aspartate transaminase (AST), lactate dehydrogenase (LDH), alanine transaminase (ALT), creatinine kinase (CK), and gold marker troponin I were determined. It was observed that there was a significant increase in the level of marker enzymes (AST, ALT, LDH, and TROPONIN) in the serum of isoprenaline-treated rats. When compared with the control group, there was an increase in the level of AST, ALT, LDH, and CK-MB in isoprenaline-induced rats. This finding could be a consequence of decrease in the number of viable myocytes due to augmented cell death in the heart as these animals showed an elevated level of AST, ALT, LDH, and CK-MB. This indicates that *T. cordifolia* could protect against myocardial damage. The mechanism in which it exerts the effect is by its potentiality to strengthen the myocardial damage by its membrane-stabilizing action [18]. Alkaloids found in other plants

Table 1: List of plants and their phytoconstituents responsible for cardioprotection

Phytoconstituents	Plant name	Family
Mangiferin [19]	*Mangifera indica*	*Anacardiaceae*
Allicin [20]	*Allium sativum*	*Amaryllidaceae*
Eugenol [21]	*Ocimum basilicum*	*Lamiaceae*
Sesamol [22]	*Sesamumindicum*	*Pedaliaceae*
Arjunolic acid [23]	*Terminalia arjuna*	*Combretaceae*
Gingerol [21]	*Zingiber officinale*	*Zingiberaceae*
Hesperidin [24]	*Citrus aurantium*	*Rutaceae*
Curcumin [25]	*Curcuma longa*	*Zingiberaceae*
Resveratrol [26]	*Vaccinium corymbosum*	*Ericaceae*
Proanthocyanidins [27]	*Crataegus oxycantha*	*Rosaceae*
α-linolenic acid [28]	*Linumusitatissimum*	*Linaceae*
Oleuropin [29]	*Oleaeuropeae*	*Oleaceae*
Ginsenosides [30]	*Panax ginseng*	*Araliaceae*
Avicularin [31]	*Polygonumaviculare*	*Polygonaceae*
Flavanoids [32]	*Myrciariacauliflora*	*Myrtacea*
Thymoquinone [33]	*Nigella sativa*	*Rananculaceae*
Lycopene [34]	*Solanumlycopersicum*	*Solanaceae*
Silymarin [35]	*Silybummarianum*	*Asteraceae*

such as *Coriandrum sativum, Newbouldia laevis, Nigella sativa,* and *Tamrindus indica* are also cardioprotective in nature [28].

Vincristine (vinca alkaloids)

Studies conducted revealed that pretreatment with vincristine (Table 2) significantly reduced the activities of marker enzymes such as CK-MB, serum glutamate pyruvate transaminase and LDH, and the levels of Troponin-T in the serum. Elimination of Isoproterenol-induced histopathological changes and reduction in myocardial necrosis were seen by transmission electron microscopy findings due to the pretreatment of vincristine. Thus, vincristine acts as a potent alkaloidal agent in attenuating isoproterenol-induced myocardial necrosis, and the probable mechanism is due to its antioxidant and free radical scavenging activities [36]. Studies explained that simultaneous vincristine treatment provided recovery of the cultured adult mouse myocytes exposed to doxorubicin. Despite the presence of doxorubicin, vincristine retains the ability to activate MAPK pathways. Acceleration of these pathways has been found to provide cardioprotection, especially after preconditioning [37]. Thus, vincristine acts as a potential agent in attenuating isoprenaline-induced cardiotoxicity and doxorubicin-induced cardiomyopathy.

Neferine

Nelumbo lucifera Gaertn, known as lotus belonging to the family *Nelumbonaceae*, is an aquatic plant from which neferine (Table 2) is obtained. Neferine is a bisbenzylisoquinoline alkaloid. The other active constituents of *N. lucifera* include roemerine, nelumbine, dauricine, liensinine, isoliensinine, lotusine, and nuciferine. Neferine constitutes the major isoquinoline alkaloid along with liensinine and isoliensinine. Previous studies reported the anticancer and anti-arrhythmic effects of *N. lucifera* [38]. Studies reported the activity of neferine against isoproterenol-induced myocardial damage, and it was found that neferine attenuates myocardial damage by acting as a strong antioxidant agent and can be used as a potent agent in oxidative stress [39]. It also toned down the increase of vascular smooth muscle cells and remarkably prevented belomycin-induced pulmonary fibrosis.

Berberine

Berberine (Table 2), obtained from *Rhizomacoptidis* belonging to the class of isoquinoline alkaloids, possesses a wide range of pharmacological activities such as antimicrobial, antidiarrheal, antidiabetic, antihyperlipidemic, anti-inflammatory, and antiproliferative effects [40]. Studies conducted revealed that berberine fortified the heart against I/R injury by improvising cardiac function, lowering myocardial apoptosis, and diminishing myocardial dysfunction. Berberine showed its action by preventing apoptosis and improving mitochondrial dysfunction following I/R [41]. Studies conducted by Lv *et al.* discovered that berberine acts as an potent compound in inhibiting doxorubicin-triggered cardiomyocyte apoptosis [42].

Saponins

Saponins are a class of phytoconstituents found in particular abundance in various plant species. They are amphipathic glycosides, structurally having one or more hydrophilic glycoside moieties combined with a lipophilic triterpene derivative. They produce foam when shaken in aqueous solution [43]. The plants such as *Terminalia arjuna, Glycyrrhiza glabra, Ilex cornuta, Crataegus oxyacantha*, and *Astragalus membranaceus* are saponin-enriched plants studied for the cardioprotective activity. Diosgenin and its derivatives which are phytosterols act as a cardioprotective agent by lowering the serum cholesterol by inhibiting the cholesterol absorption in the intestinal tract [44]. Saponins' cardioprotective potential was observed by different pharmacological effects such as antioxidant, anti-hypoxic, anoxia/reoxygenation, Ca^{2+} ion regulation or calcium antagonist, cardiocyte apoptosis, vasodilatory effect, and angiogenesis, as summarized in Fig. 1 [45].

Diosgenin (Table 2) acts as a good antihyperlipidemic agent. It promotes bone development by significantly elevating the production and secretion of Type I collagen [46]. Earlier studies reported the use of diosgenin in attenuating isoproterenol-induced myocardial damage. Due to its antioxidant property [17], this reversed the membrane-bound enzyme activity and hence helped in maintaining the electrolyte concentration which was the possible mechanism in which it showed its cardioprotective activity [47]. Anti-carcinogenic and antiviral activities [44] of diosgenin were reported earlier, and this was due to its ability in significantly lowering the viral ribonucleic acid and viral proteins [48].

Glycyrrhizic acid

Glycyrrhizic acid (Table 2) is the major therapeutic constituent obtained from the root extract of the plant *G. glabra,* also known as liquorice, a shrub from *Leguminosae* family. It is a triterpene saponin glycoside. Studies revealed that glycyrrhizic acid shows different pharmacological action such as anti-ulcer, expectorant, antiviral, anti-inflammatory, antidiabetic, neuroprotective, and immune-enhancing properties. *In vivo* studies revealed that glycyrrhizic acid possesses antioxidant properties and gives protection against isoproterenol-induced myocardial damage. The possible mechanism in which it exerts action is due to its antioxidant nature and also by a significant reduction in the levels of lipid hydroperoxides and isoprostanes and significant increase in the levels of superoxide dismutase (SOD) and glutathione (GSH) level [49].

Sulfur-containing compounds

Allicin (Table 2), an organosulfur compound, is obtained from *Allium sativum* which is commonly known as garlic belonging to the family *Amaryllidaceae*. When fresh garlic is chopped or crushed, the enzyme alliinase converts alliin into allicin, which is responsible for the characteristic aroma of fresh garlic. The allicin formed is unstable and quickly converts into a series of other sulfur-containing compounds such as diallyl disulfide. Allicin is part of a defense mechanism against attacks by pests on the garlic plant [8]. *A. sativum,* also known as garlic, is said to have originated 6000 years ago and was considered as a good therapeutic potential for treating cardiovascular problems. Other therapeutic properties of this plant include antimicrobial and anticancer and treating other health disorders. In olden days, garlic was used as a good flavoring agent. From the previous studies, two studies reported the efficacy of garlic in the prevention of cardiac hypertrophy in *in vivo* models of hypertension and diabetes. However, the mechanism in which it showed their actions has not been explored [50]. Preclinical and clinical studies have shown that daily intake of garlic as a food supplement reduces cholesterol and blood pressure along with the inhibition of platelet aggregation. It has also been reported that the vascular function is improved; however, more researches need to

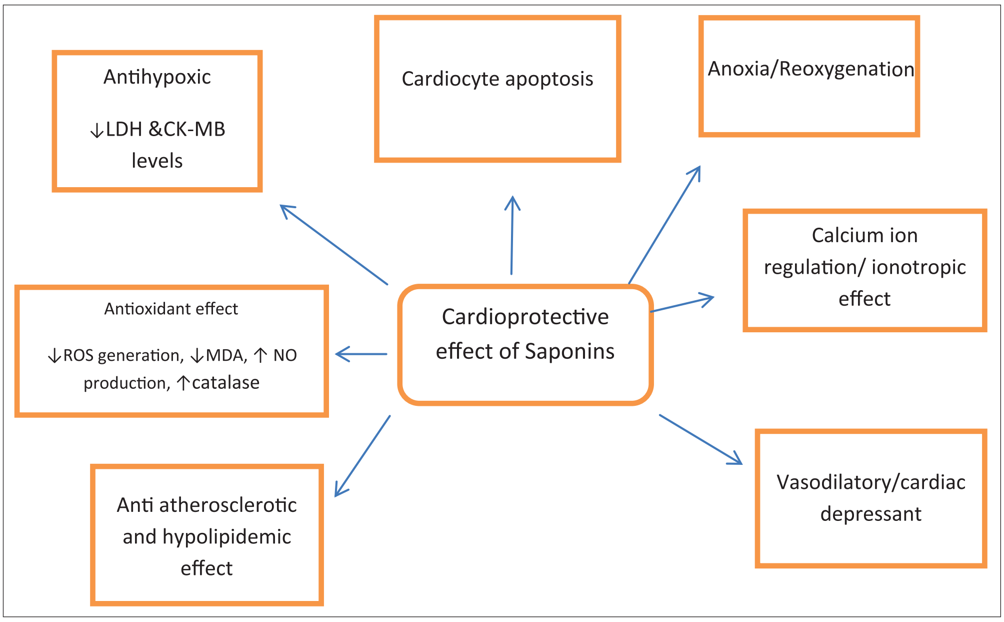


Fig. 1: Mechanism in which saponins show cardioprotection

be done in this area to elaborate on its cardiovascular property. The influence of garlic on heart health is due to the presence of its active metabolite allicin and its breakdown into organic polysulfides. It is hypothesized that hydrogen sulfide may have an important role in garlic-induced cardiac protection. The foremost mechanism by which garlic supplements H_2S bioavailability is via alteration of garlic-derived polysulfides. Organic sulfides present in high concentrations in garlic interact readily with thiol groups or thiol-containing compounds (i.e., GSH) present in biological systems to generate free H_2S. Advanced research suggests that the cardioprotective role of garlic depends on the consumption of the different preparations such as raw garlic, aged garlic, garlic powder, and garlic oil [51].

Essential oils

Essential oils are also called volatile oils, ethereal oil, or the oil obtained from the plants. They are usually concentrated liquid which are hydrophobic in nature containing volatile aromatic compounds of the plants. They are often referred as essential oils because it contains the "essence" of the plant fragrance, the characteristic fragrance of the particular plant. The methods of extracting the essential oils from plants include mainly steam distillation followed by expression, solvent extraction, absolute oil extraction, resin tapping, wax embedding, and cold pressing. Essential oils are often used in aromatherapy or as an alternative medicine in the treatment of diseases, and the activities shown are due to the presence of compounds responsible for aroma [52]. The commonly available plants from which volatile oils are obtained include coriander, clove, ginger, mentha, spearmint, peppermint, cedar wood, eucalyptus, lemon, cinnamon, and tulsi.

Linalool

Lavandulaangustifolia, commonly known by the name English Lavender or True Lavender, is a flowering plant belonging to the family *Lamiacea*. Lavender oil obtained from the plants mainly consists of linalyl acetate, linalool (Table 2), 1,8-cineol, lavandulol, lavandulyl acetate, camphor, cis-β-ocimene, trans-β-ocimene, 1-terpinen-4-ol, α-terpineol, limonene, tannins, coumarins, flavonoids (luteolin), phytosterols, and triterpens [53,54]. *L. angustifolia* has been used for its wide therapeutic properties such as carminative, diuretic, antiepileptic, antirheumatic and pain reliever, especially in nervous headache and migraine [55]. Lavander essential oil is believed to show potential therapeutic activity against stress, anxiety, exhaustion, irritability, insomnia, depression, colds, digestion, flatulence, upset stomach, liver and gallbladder problems, nervousness, and loss of appetite [56]. The mechanism of action through which the essential oil of *L. angustifolia* exerts its effect is by anti-inflammatory, free radical scavenging, and antioxidant activities [57]. Thus, from the *in vivo* studies conducted, it was concluded that the essential oil of *L. angustifolia* showed cardioprotective activity by normalizing ECG, improving the hemodynamic impairment, reducing LPO, inhibiting pro-inflammatory responses, and boosting the antioxidant defense systems. Essential oil of lavandula maintained the structure and architecture of cardiac cells by decreasing cardiac tissue damage and strengthening myocardial membrane as evident from the histopathological results of myocardial tissue [58].

Coriandrol

Other plants containing essential oil in which cardioprotection has already been reported include *Coriandrum sativa*, which belongs to the family *Apiaceae* commonly known by the name cilantro having the major active constituent coriandrol (Table 2), mainly shows its mechanism of action by the significant reduction in the levels of total cholesterol (TC) and triglycerides (TG) [59]. In an another study, there was a notable decrease in the levels of TC, TG, TAG, and low-density lipoprotein (LDL) cholesterol in plasma and a consequential increase in the level of high-density lipoprotein cholesterol plasma which is discovered in the cholesterol-rich (1%) basal diet-fed rats treated with coriander seed oil [60]. Antiplatelet activity of the leaf extract of *C. sativum* leaves and curry leaves was monitored at varying concentrations on human platelets, which showed the inhibition of platelet aggregation [61].

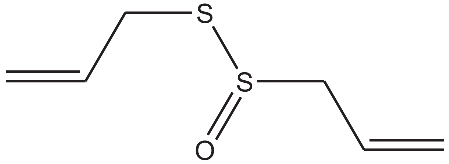
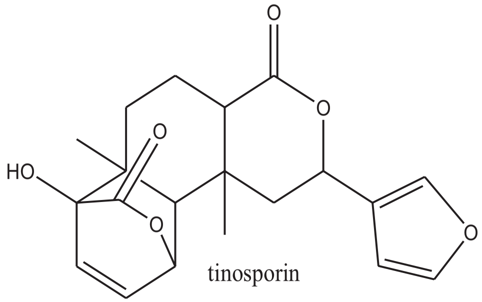
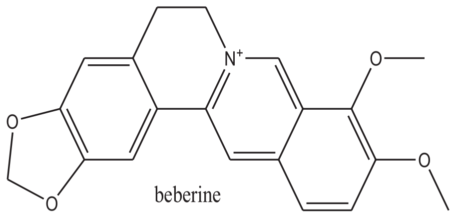
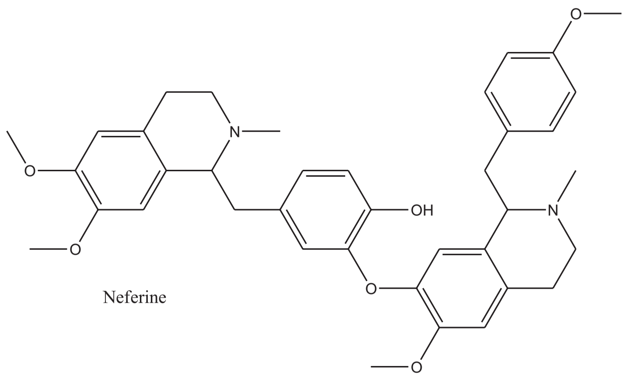
Gingerol

Zingiberofficinale, also known as ginger belonging to the family *Zingeberaceae* and containing the essential oil gingerol (Table 2), is responsible for relaxing the blood vessels, relieving pain, and stimulating blood flow. This acts as a potent anti-inflammatory agent, and hence it is useful in the treatment of cancer, heart diseases, and neurodegenerative disorders such as Alzheimer's disease [61]. Other plants containing volatile oils include cinnamon, black pepper [55], and saffron [62] in which cardioprotective activity has been reported.

Omega fatty acids

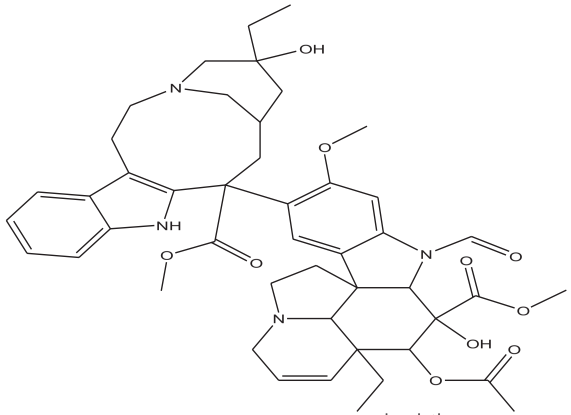
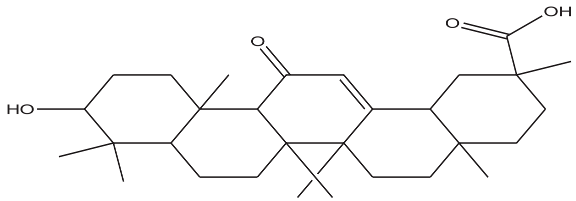
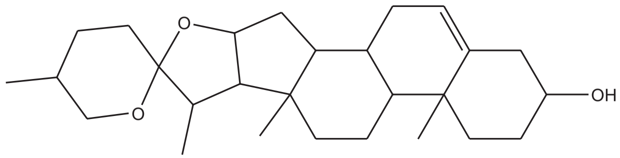
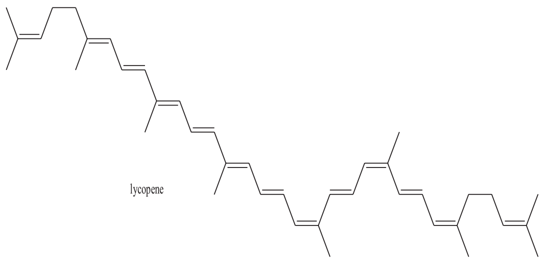
Omega fatty acids are a class of polyunsaturated fatty acids, with the exception being omega 9 fatty acid which is a monounsaturated fatty acid, i.e., having only one double bond. The different omega fatty acids include omega 3 fatty acids, omega 6 fatty acids, and omega 9 fatty acids. The source of omega 3 fatty acids includes salmon, mackerel, sardines, and chia seeds walnuts. Omega 6 fatty acids are obtained from soybean

Table 2: Summary of phytoconstituents structure, class, effect and mechanism of action

Phytoconstituents and their source	Class	Structure	Effect	MOA
Allicin Source: *Allium sativum*	Sulpher containing compound	 allicin	↓CK-MB, LDH, AST, ALT, HMG CoA reductase	↑H_2S bioavailability resulting in Nitric oxide signalling
Tinosporin Source:-*Tinoporacordifolia*	Alkaloids	 tinosporin	↓AST, ALT, CK-MB, LDH Reduces infarct size	Strengthen myocardial damage by its membrane stabilising action
Berberine Source:- *Rhizomacoptidis*	Alkaloids	 beberine	↓Myocardial apoptosis and necrosis↓ Myocardial IL-6 accumulation and TNF-α production	Preventing apoptosis, improving mitochondrial dysfunction, partial mechanism by SIRT1 signalling
Neferine Source:- *Nelumbolucifera*	Alkaloids	 Neferine	↓Serum marker enzymes, lipid peroxidation	Strong antioxidant defense system

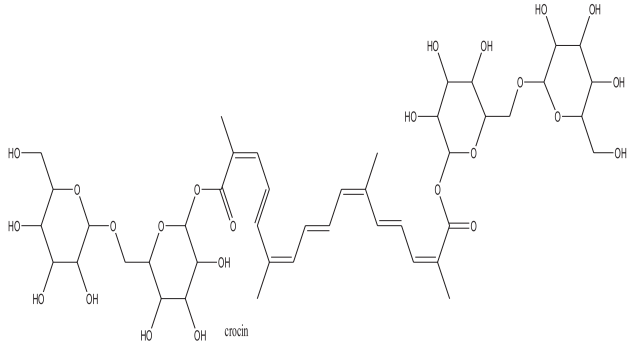
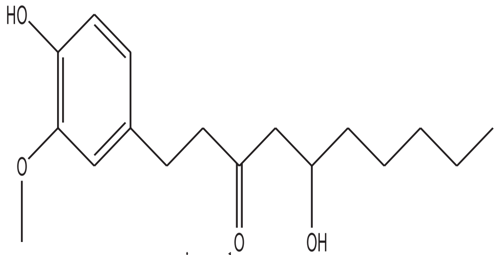
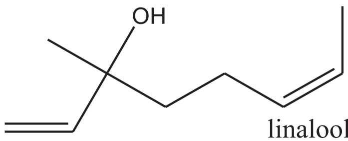
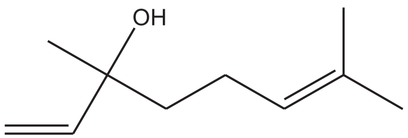
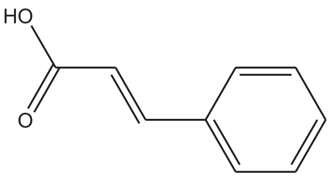
(Contd...)

Table 2: *(Continued)*

Phytoconstituents and their source	Class	Structure	Effect	MOA
Vincristine	Alkaloids	 vincristine	↓Marker enzymes CK-MB, serum gutamate pyruvate transaminase, LDH, levels of Troponin-T	Antioxidant defense system and free radical scavenging
Glycyrrhizic acid Source:- *Liquoriceglabra*	Triterpenesaponin glycoside	 glycyrrhizic acid	↓Lipid hydroperoxides and isoprostanes	Antioxidant agent
Diosgenin	Steroidal saponin	 Diosgenin	Decrease in CK-MB and βglucuronidase, β-N-acetyl glucosaminidase, activity. Increase in Na+/K+ATPase	Antioxidant agent, anti hyperlipidemic agent
Lycopene Source: Tomatoes, red carrots, watermelon, papaya	Carotenoid	 lycopene	↓Cardiac LDH, platelet aggregation, serum marker enzymes	Anti-oxidant defense system and hypolipidemic action

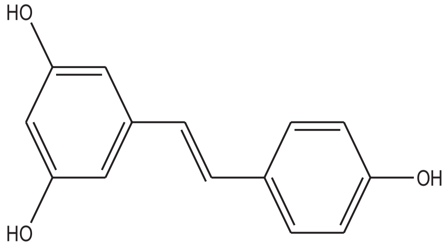
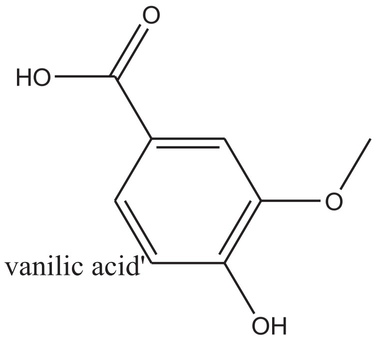
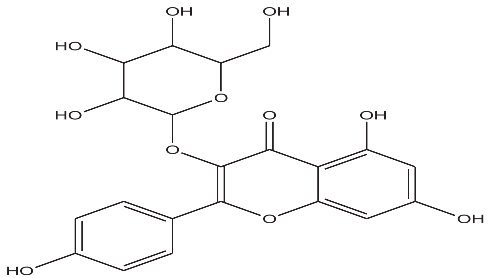
(Contd...)

Table 2: *(Continued)*

Phytoconstituents and their source	Class	Structure	Effect	MOA
Crocin Source:-*Crocus sativa*	Carotenoid	 crocin	↓SOD, CK-MB isoenzymes, reduced glutathione, along with↑malondialdehyde ,↓serum TG, VLDL, total cholestrol	Modulation of oxidative stress by maintaining redox status of cell, Pancreatic lipase inhibition
Gingerol Source: *Zingiberofficinalae*	Essential oil	 gingerol	Relaxation of blood vessels relieve pain and stimulate blood flow	Anti-inflammatory agent
Linalool Source: *Lavender angustifolia*	Essential oil	 linalool	Normalising ECG, improvinghaemodynamicparameters, ↓lipid peroxidation	Free radical scavenging, antioxidant activity, inhibiting pro inflammatory responses
Coriandrol Source: *Coriandrumsativum*	Essential oil	 coriandrol	↓ Total cholestrol, TG, TAG, LDL-c,↑HDL-c	Antioxidant defense system
Cinnamic acid	Polyphenol	 cinnamic acid	↑Serum nitric oxide↓ creatininekinase, LDH, TNF-α, interleukin and malondialdehyde	Antioxidant defense system and free radical scavenging effect

(Contd...)

Table 2: ***(Continued)***

Phytoconstituents and their source	Class	Structure	Effect	MOA
Resverastrol Source: Red wine, Grapes, Peanuts, Cranberries, Chocolates	Polyphenol	 resveratrol	Decrease apoptotic death, ↓ lipid peroxidation, ↓inflammatory mediators	Role of nitric acid is prime mechanism along with up-regulation of inducible NO synthase, vascular endothelial growth factor
Vanilic acid Source:- Vanillin	Polyphenol	 vanilic acid'	Protective effect on cardiac troponins, ECG, lipid peroxidation and expression of interleukin-1β, interleukin 6 and TNF-α	Antioxidant defense system
Astragalin	Flavanoids	 astragalin	↓MDA, TNF-α, IL-6, ROS and Bax and↑GSH/GSSG	Reducing intracellular oxidative stress and apoptosis
Linolenic acid Source: Fish, seeds such as walnuts, sunflower seeds, pumpkin seeds		 linolenic acid	↓Atherosclerotic plaque,↑ β-oxidation	Anti-inflammatory agent Anti-thrombotic effect, hypzo triglyceridimic effect

AST: Aspartate transaminase, LDH: Lactate dehydrogenase, ALT: Alanine transaminase, CK: Creatinine kinase, MDA: Malondialdehyde, TNF: Tumor necrosis factor, ECG: Electrocardiographic, TG: Triglycerides, TAG: Triacylglycerol, ROS: Reactive oxygene species, VLDL: Very low density lipoproteins, LDL: Low density lipoproteins, HDL: High density lipoproteins oil, corn oil, walnut, sunflower seeds, cashew nuts, etc. The sources from which omega 9 fatty acids are obtained include olive oil, almond oil, peanut oil, walnut, cashew, etc. [63]. Omega 3 fatty acids (Table 2) belong to a class of polyunsaturated fatty acids. The omega 3 fatty acids are concerned fundamentally with CV health are marine obtained eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The primary source includes fish oil and seafood which are obtained from the marine microorganisms which transmit through food chain. The plant-procured omega 3 fatty acids include linolenic acids which are further converted to EPA and DHA, but their role on cardioprotection is less clear than that of EPA and DHA [64]. It was presumed that the capability of these dietary fatty acids to exert pleotropic effects in cells and tissues is because they are embedded in the phospholipid of cellular membranes [65], resulting in the subsequent alteration of the physicochemical properties such as deformability, permeability [66], and fluidity. The anti-inflammatory and anti-thrombotic effects of omega 3 fatty acids have been related to the metabolic conversion of their oxygenated derivatives which are predominantly named as oxylipins which are highly bioactive factors acting at very low concentrations [67]. The increased formation of specific LC-omega-3-PUFA is thought to decrease the atherosclerotic plaque formation and induce their stabilization by decreasing the infiltration of inflammatory and immune cells. The capability of ω-3 PUFA to hinder the production of very LDLs (VLDLs) from the liver, as well as the transformation of VLDL to intermediate-density lipoprotein and LDLs, has been related to their hypotriglyceridemic effect. On the other hand, this effect has also been explained based on the potency of ω-3 fatty acids to increase β-oxidation, thus leading to the depletion of the fatty acid substrate for triglyceride synthesis [68].

Carotenoids

Carotenoids, also known by the name tetraterpenoids, belong to a class of organic pigments commonly synthesized from plants, algae, bacteria, fungi, and are also present in foods such as fruits, vegetables, and fish. They are liposoluble pigments which are colorful in nature. Carotenoids include β-carotene, α-carotene, lycopene, lutein, and cryptoxanthin. Carotenoids are responsible for the yellow, orange, and green color of fruits, flowers, and vegetables. Epidemiological studies conducted revealed that diet rich in carotenoids lowers the incidence of cancer, osteoporosis, CVDs and age-related macular degeneration, cataract, and infectious diseases such as HIV. The cardioprotective potential of carotenoids by altering various parameters is summarized in Fig. 2 [69].

Crocin

Crocus sativus L, a stemless herb commonly known by the name Saffron, is a member of the family *Iridaceae*. The pharmacologically active components of *C. sativus* include Saffranal, crocin, crocetin, and picrocrocetin. The major constituent of the essential oil of saffron includes Saffranal which is a monoterpene aldehyde and this, in particular, is responsible for the characteristic odor and aroma. The effects of crocin (Table 2), a pharmacologically active constituent of *C. sativus* L., in isoproterenol (ISO)-induced cardiotoxicity, were determined with reference to hemodynamic, antioxidant, histopathological, and ultrastructural parameters [55]. *In vivo* studies conducted with varying doses of aqueous saffron extract revealed a marked reduction in the levels of CK-MB isoenzyme, LDH, SOD, and reduced GSH along with an increase in the level of malondialdehyde (MDA). Under light microscopy, myocardial necrosis, edema, and inflammation were evident. Further, the protective role of crocin on ISO-induced myocardial damage was reconfirmed by histopathological and ultrastructural studies. Thus, the protective role of crocin in myocardial damage was more pronounced, and the mechanism in which it shows the action was by the modulation of oxidative stress by maintaining the redox status of the cell [70]. On administering aqueous extract of saffron, a remarkable reduction in the serum TGs, TC, and VLDL-cholesterol was observed. The hyperlipidemia effect of crocin was due to its pancreatic lipase inhibition [71].

Lycopene

Lycopene (Table 2), a red carotenoid pigment, is present abundantly in vegetables such as tomato, red carrot, watermelon, and papaya. Studies on lycopene revealed that it is the most efficient singlet oxygen quencher and peroxyl radical scavenger than other carotenoids and way better effective than α-tocopherols. Studies have reported that lycopene protects adrenaline-induced MI, coronary artery disease, along with hypolipidemic and antioxidant activities. Studies have reported that simultaneous administration of Lycopene and Vitamin E has shown a decrease in the levels of cardiac marker enzymes, endogenous enzymes, membrane bound enzyme levels along with histopathological changes [72].

Polyphenols

Natural polyphenols are the broadest group of phytochemicals that gained much popularity as a potent candidate in the prevention of oxidative stress-related diseases such as diabetes, neurodegenerative disorders, cancer, CVDs, and aging [73,74]. They are secondary metabolites of plant, and the major source is plant-based foods. Polyphenols possess effect on bitterness, astringency, color, flavor, odor, and oxidative stability of food. Polyphenols act as potent antioxidant, anticancer, anti-aging, anti-inflammatory agent, and even show antimicrobial actions [30]. Polyphenols are generally divided into

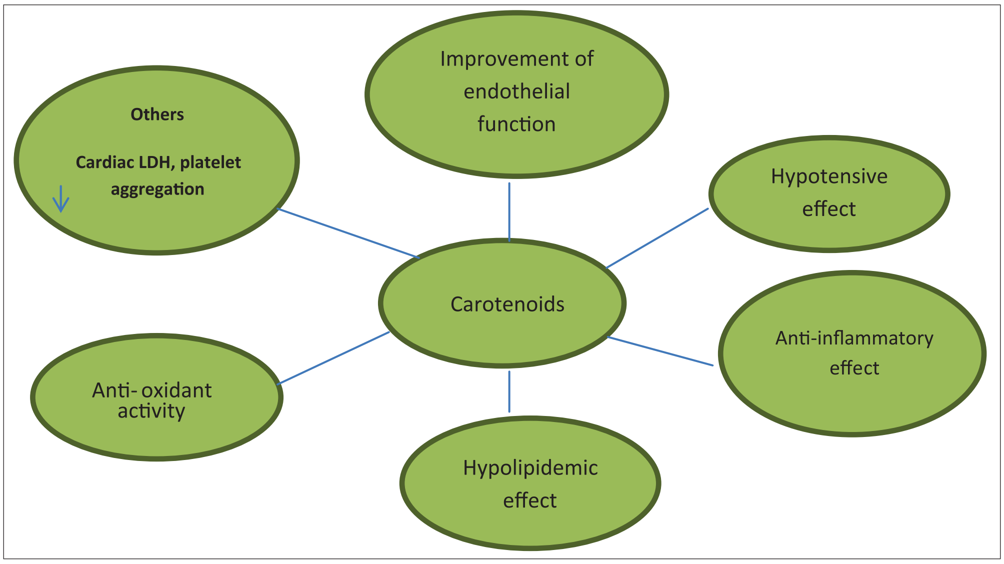


Fig. 2: Cardioprotective activity of carotenoids

flavanoids and nonflavonoids: catechin, quercetin, proanthocyanidins, condensed tannins, and anthocyanins belong to flavanoids and hydrolyzable tannins, and benzene and cinnamate derivatives fall under nonflavanoids.

Cinnamic acid

Hydroxycinnamic acids (Table 2) are the prime class of polyphenols seen in every plant. The most indicative hydroxycinnamic acid is caffeic acid (3, 4-dihydroxy cinnamic acid) commonly seen in fruits, grains, and dietary supplements. It acts as a chelator of metal ion and shows free radical scavenging and antioxidant effects. *In vivo* studies conducted revealed that caffeic acid preserved the cardiac mitochondrial structure along with its functions in isoproterenol-induced MI. *In vitro* studies of caffeic acid revealed the free radical scavenging activity. The probable mechanism in which caffeic acid showed action is due to its antioxidant effect and free radical scavenging activity [75].

Resveratrol

Resveratrol (Table 2) belongs to the class of polyphenol which is beneficial to health in many ways because it has antioxidant and anticancer properties and also used in the treatment of CVDs. This is found in foods such as peanuts, pistachios, grapes, red wine, white wine, cranberries, blueberries, dark chocolate, and white chocolate [76]. *In vivo* studies demonstrated that pretreatment of RES resulted in protection against the deleterious effects of myocardial reperfusion after ischemia, especially by reducing the infarct size and decreasing arrhythmias. The role of nitric oxide (NO) is one of the prime mechanisms of pharmacological prerequisite by resveratrol. A current study proposed that the coordinated upregulation of inducible NO synthase, vascular endothelial growth factor, kinase insert domain-containing receptor, and endothelial NO synthase is one of the resveratrol's essential mechanisms. Resveratrol attenuates various soluble intercellular cytokines such as ICAM, VCAM, and E-selectin through upgrading the endothelium function, which lessens the infarct size [77]. Resveratrol also shields the heart by acting as a potent antioxidant by scavenging free radicals and inhibiting LPO both *in vitro* and *in vivo* [72].

Vanilic acid

Vanilic acid (Table 2), a polyphenolic acid, is the oxidized form of vanilin which is a widely used compound in drug, cosmetic, and food industries having various pharmacological activities such as antitumor [78], anti-melangogenesis [79], and anti-angio genetic [80]. Vanilic acid acts as a natural antioxidant agent [81]. *In vivo* studies conducted revealed that pretreatment with vanilic acid showed significant protective effect on cardiac troponins, electrocardiogram, LPO, and expression of interleukin (IL) IL-1β, IL-6, and tumor necrosis factor (TNF)-α gene in isoprenaline-induced cardiotoxicity in rats. The reduction in the size of infarct was also observed. The mechanism in which vanilic acid showed its effect is due to its possible antioxidant defense system [82].

Flavanoids

Flavanoids are structurally diverse and most abundant polyphenols. They are found in the form of glycosides and aglycosides. Flavanoids are divided into various subclasses which include flavanols, flavanones, flavones, isoflavones, and anthocyanidins. They are found in foods such as dark chocolates, red wine, citrus fruits, parsley, bananas, green tea, and onions with the content of 70% or more. The mechanisms of action of flavanols to show cardioprotective activity include antioxidant effect, modulation of cell signaling and gene expression, and modification of cell membrane properties and receptor function. In addition to the abovementioned properties, it can inhibit enzymatic activities [83].

Astragalin

Astragalin (Table 2), a bioflavonoid obtained naturally, has been well known for its pharmacological activity. It has been reported to exhibit multiple pharmacological properties including antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective properties. The role in cardioprotective mechanism is due to the regulation of bradykinin, adenosine, opioid, adrenergic, and other G-protein-connected receptors. Astragalin was proved to be effective against acute ischemic reperfusion injury in Sprague–Dawley rats as its mechanism of action proceeds via reducing intracellular oxidative stress and apoptosis. The mechanism includes reduced expression of MDA, TNF-α, IL-6, reactive oxygen species, and Bax along with the increased ratio of GSH/ oxidised glutathione (GSSG), respectively [84].

Newer perspective

CVDs, predominantly MI, is the leading cause of death globally. The increase in death rate is due to certain risk factors such as smoking, obesity, age, cholesterol, family history, diabetes, and sedentary lifestyle including lack of exercise and healthy food habits. The Statistics on Myocardial Infarction 2016 revealed that approximately 25,700 people suffered from an attack of acute MI. The study also revealed that the number of attacks and mortality rate in the public increases with age. Until the end of the 21st century, mortality rate has been higher among men than among women regardless of education level. However, in recent years, mortality rate for men with postsecondary education is lesser than that for women with compulsory education. The treatment includes in MI is advanced and uses various methods and medication. The present-day treatment includes myocardial reperfusion where coronary thrombi were lysed by infusing streptokinase directly into the blocked coronary arteries of patients suffering from MI. In the past few years, myocardial reperfusion has advanced and, in addition to the use of aspirin, other antiplatelet agents to the fibrinolytics and stents – first being bare metals followed by drug-eluting stents – are on use. It is clearly observed that, along with the higher incidence of occurrences of diseases, the advancement in the treatment has been on point. However, as the saying goes "Prevention is better than cure," the incidence of occurring can be prevented with the help of nature. The above information revealed that nature is the best therapy because it contains various plants and plant-derived principles abundantly present in various forms. There are different ways in which the occurrence of disease can be prevented. It can be observed that, plant-derived principles in different formulations can give a secondary protection to the myocardial tissues and can act as a supplement in aiding in the prevention of diseases. Usage of certain plants as a part of diet can improve the blood circulation, purify the blood, reduce the cholesterol level, and overall maintain a healthy body conditions. The field still remains open for the exploration of plant-based formulations that can not only offer protection against MI, but also serve as a therapeutic formulation to reverse the effects responsible for MI.

CONCLUSION

The findings of the study may help in elucidating the clinical mechanisms and effects of phytoconstituents underlying the valuable effects of plant-derived principles on CVDs, by the modulation of various cardiovascular risk factors such as oxidative stress, atherosclerosis, hyperlipidemia, and inflammation. Despite the previous studies in this area, this is a concise review which also considers the molecular mechanism of plant-derived principles in the cardiovascular system. Nevertheless, further systematic review and analysis are required to elucidate the exact mechanism of the beneficial effect.

AUTHORS' CONTRIBUTION

The first author contributed in the conceptualization of the article along with the collection of data and preparation of manuscript. The corresponding author provided expertise and feedback.

CONFLICT OF INTERESTS

We declare that we have no conflicts of interest.

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