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Spices, Fruits, Nuts and Vitamins: Preventive Interventions for Myocardial Infarction

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ABSTRACT

Background: In spite of availability of effective interventions, the mortality rate due to myocardial infarction in cardiovascular and metabolic disease patients is progressively increasing. Numbers of therapeutic agent are presently employed for the prevention and management of myocardial infarction include beta blockers, anti-thrombotics, thrombolytics, statins, angiotensin converting enzyme inhibitors, angiotensin-II receptor blockers, calcium channel blockers and nitrovasodilators. Patients with hypertension, atherosclerosis and diabetes mellitus are major risk of myocardial infarction. Thus, there has been a regular need to develop effective therapies for the prevention and management of this insidious disease in cardiovascular patients. **Results:** There are number of herbal and synthetic pharmacological interventions which have been shown to prove preventive effect in experimentally-induced myocardial infarction. **Conclusion:** This review is framed to enlighten numerous herbal interventions targeting to mollify myocardial oxidative stress, inflammation, loss of myocytes and subsequently acute myocardial infarction.

Key words: Inflammation, oxidative stress, myocardial infarction, herbs, vitamins, spices, nuts

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INTRODUCTION

Ischemic heart disease is a major leading cause of morbidity and mortality. Its prevalence is instantly increasing worldwide (Kalra and Roy, 2012; Veinot *et al*., 2012). Myocardial infarction occurs as a result of coronary artery obstruction, thrombotic occlusion and coronary vasospasm associated with myocardial ischemia (Horimoto *et al*., 1993; Martin *et al*., 2012). High oxidative stress and inflammation plays a key role in the pathogenesis of myocardial infarction (Ueda *et al*., 2011; Yang *et al*., 2012). Acute myocardial infarction is associated with various symptomatic alterations such as sudden chest pain radiating to the left arm and shoulder, shortness of breath, anxiety, palpitation, sweating, vomiting and nausea (Upaganlawar *et al*., 2011).

In myocardial ischemic condition, generation of reactive oxygen species (ROS) plays a key role in cardiac physiology and pathophysiology (Filippo *et al*., 2006) (Fig. 1). ROS are mainly produced in endothelial cells by xanthine oxidase in cardiomyocytes by mitochondrial electron transport chain reactions and in inflammatory cells by nicotinamide adenine dinucleotide phosphate oxidase (NADPH) (Waypa *et al*., 2002) (Fig. 1). This oxidative stress leads to damage of macromolecules, proteins and deoxyribonucleic acid. The increment in oxidative stress is also mediated by imbalance of antioxidant defense mechanism. Decrease levels of antioxidant enzymes Superoxide dismutase (SOD), catalase and glutathione peroxidase results myocardial infarction (Palanisamy *et al*., 2009). Reduced glutathione (GSH) levels protect cell injury induced by generated peroxides and through ROS generating reactions. Induction of high oxidative stress in the heart is one of the key events that could contribute to isoproterenol-induced experimental myocardial infarction (Rathore *et al*., 1998; Rajadurai and Prince, 2006).

Inflammation, a complex whole-cellular pathway begins with the production of excess free radicals that frequently arise from mitochondria responding to internal or environmental stress. Nuclear factor-κB (NF-κB), a transcription factor upregulates the production of downstream inflammatory mediators including Inducible nitric oxide synthase (iNOS), Cyclooxygenase-2 (COX-2), pro-inflammatory cytokines i.e., Tumor necrosis factor-alpha (TNF-α) and Interleukein-1beta (IL-1β), Interleukin-6 (IL-6) (Mann and Young, 1994; Mann, 2002) (Fig. 1). Pro-inflammatory cytokines are also involved in cardiac

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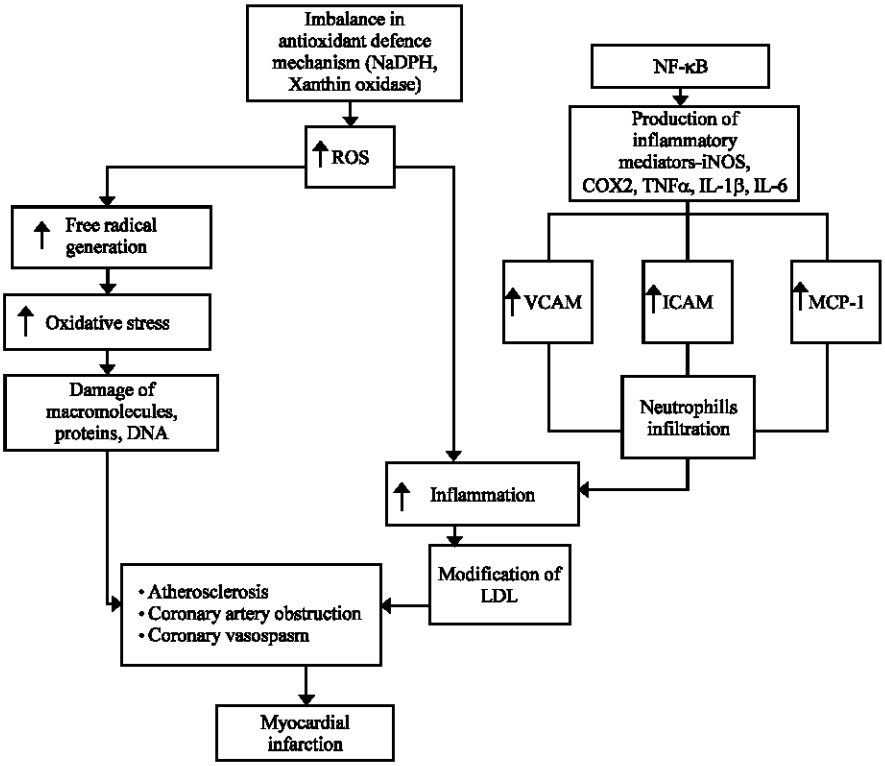

Fig. 1: Pathophysiological role of oxidative stress and inflammation in myocardial infarction. This flow-chart represents increased biomarkers of myocardial infarction during oxidative stress and inflammation. ↑Represent increased, ROS: Reactive oxygen species, MCP: Monocyte chemo attractant protein, IL-1β: Interleukein-1beta, IL-6: Interleukin-6, IL-8: Interleukin-8, TNFα: Tumor necrosis factor-alpha, NF-κB: Nuclear factor-κB, iNOS: Inducible nitric oxide synthase, COX-2: Cyclooxygenase-2, VCAM-1: Vascular cell adhesion molecule-1, ICAM-1: Intercellular adhesion molecule-1

muscle dysfunction and in the complex syndrome of heart failure (Mann and Young, 1994; Mann, 2002; Torre-Amione, 2005; Blum, 2009). Ischemic stress is a trigger for release of cytokine in the acute post infarction period includes mechanical deformation, ischemic stimulus, ROS and cytokine self-amplification pathways. Increased inflammatory responses and cytokine increments are particularly active after myocardial infarction (Nian *et al*., 2004). Inflammation is also a key factor in all aspects of coronary disease including the initiation and progression of atherosclerotic plaque, plaque rupture and thrombosis (Pashkow, 2011). NF-κB, proinflammatory cytokines and TNF-α mediates expression of Vascular cell adhesion molecule-1 (VCAM-1) that binds monocytes and T lymphocytes, the types of leukocytes found in early atherosclerotic plaques lesions (Libby, 2006) (Fig. 1). Neutrophils infiltration is also regulated by proteins like selectin and integrin that mediates leukocyte rolling and adhesion with Intercellular adhesion molecule-1 (ICAM-1) in endothelium, generating cytotoxic effect (Sellak *et al*., 1994) (Fig. 1). Beside inflammatory factors, elevated serum lipids have also been shown to be a major risk factor for the development of coronary heart disease and atherosclerosis (Kabiri *et al*., 2010). Oxidative modification of Low Density Lipoprotein (LDL) also plays a pivotal role in the progression of atherosclerosis (Joshi and Joshi 2007).

However, herbal drugs have been an integral part of society since the beginning of human civilization. These herbal medicine lost ground to the new synthetic medicines. But now days, they are gaining greater acceptance from the public and the medical profession due to greater advances in understanding the mechanism of action by which herbs can positively influence health and quality (Raza *et al*., 2012; Fugh-Berman, 2000). Thereby, this review discuss information gleaned for various herbal drugs suggesting that adding herbs to daily life serve as scrumptious and sensible way to keep heart healthy.

Allium sativum: *Allium sativum* (Garlic), a potent therapeutic herbal drug used for its ameliorative activity viz., immunomodulatory, anti-microbial, anti-neoplastic and cardioprotective, belongs to family Lilliaceae (Jalali *et al*., 2008; Jafari *et al*., 2009). The garlic homogenate has been widely accepted agent for prevention and treatment of metabolic disorders associated with cardiovascular system such as atherosclerosis, arrhythmia, hyperlipidemia, thrombosis and hypertension (Banerjee and Maulik, 2002; Khan *et al*., 2008; Karim *et al*., 2011). Allicin was earlier thought to be the major bioactive compound in garlic that is responsible for the cardioprotective effect but garlic also attributes cardioprotection due to its other active organosulfur metabolite such as S-allylcysteine and S-allylmercaptocysteine which have potent antioxidant effects (Imai *et al*., 1994; Ide and Lau, 1997) (Fig. 2). *In-vitro* studies conducted by Gebhardt and Beck (1996) also revealed that water soluble organosulfur compounds, especially S-allylcystine present in AGE and diallyldisulfide present in garlic oil are also potent inhibitors of cholesterol synthesis (Gebhardt and Beck, 1996; Banerjee and Maulik, 2002) (Fig. 2). Moderate doses of *Allium sativum* augments the endogenous antioxidants activities and depletes the oxidative damaging effects either by increasing the synthesis of endogenous antioxidants or decreasing the generation of oxidants (Banerjee *et al*., 2002). Anti-platelet mechanism of *Allium sativum* is also well established whereas, aqueous extract of *Allium sativum* also inhibit platelet aggregation induced by Adenosine diphosphate (ADP), collagen, arachiodionic acid, epinephrine and calcium ionophore in dose dependent manner (Srivastava, 1986). *Allium sativum* attributes the potent anti-atherosclerotic activity by reducing the lipid content in arterial wall (Orekhov and Grunwald, 1997) (Fig. 2). Lipogenic and cholesterogenic enzymes [fatty acid synthase, malic enzyme, glucose-6 phosphate dehydrogenase and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase activities have been significantly reduced by garlic (Yeh and Liu 2001). Age garlic extract at the dose of 250 mg kg^{-1}, when administered to doxorubicin induced Wistar albino rats reduce the elevated levels of serum cardiac enzymes LDH and CPK and MDA in plasma (Alkreathy *et al*., 2010). In conclusion the use of *Allium sativum* in diet is defensible against cardiovascular manifesting myocardial infarctions. All the deleterious cardiac changes induced by isoproterenol (decrease in endogenous antioxidants i.e., myocardial catalase, GSH and GPx activity and mitochondrial enzyme activities like citrate synthase and β hydroxyacyl CoA dehydrogenase) were significantly attenuated by aqueous garlic homogenate (250 and 500 mg kg^{-1} day^{-1} orally) administered for 30 days to mice. Authors suggested that the effect was mediated by garlic induced Nitric Oxide (NO) formation (Khatua *et al*., 2012) (Table 1).

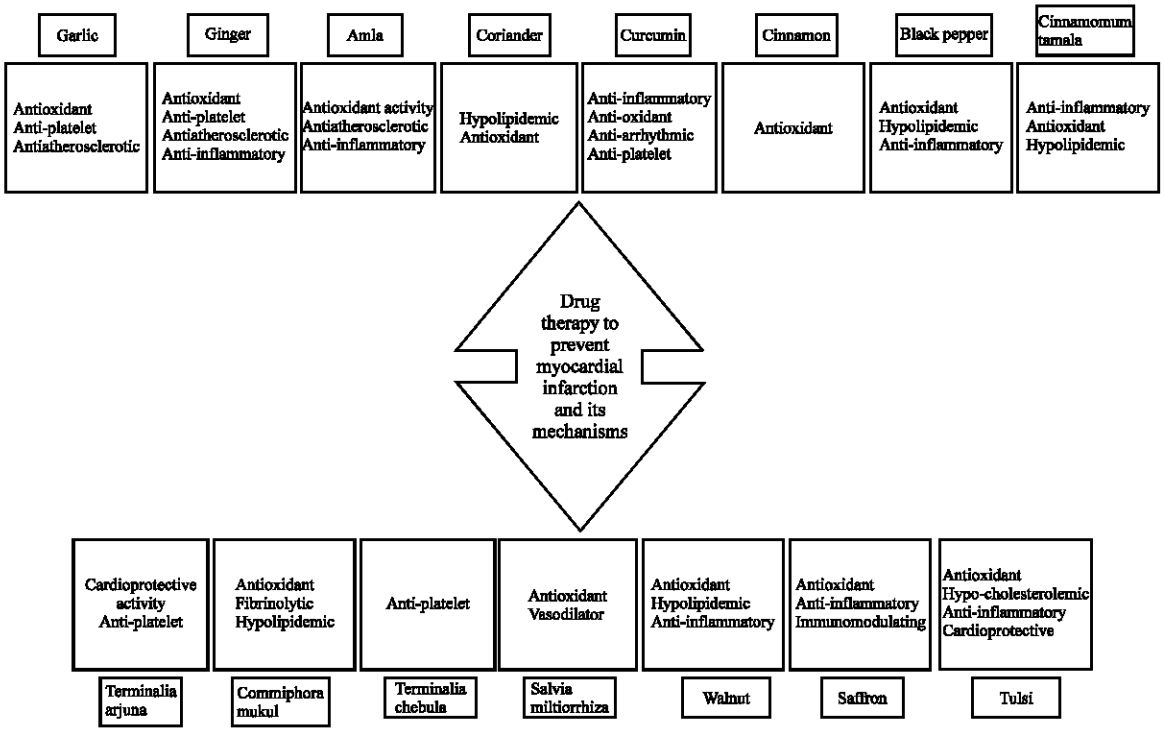

Fig. 2: Drug therapy to prevent myocardial infarction and its mechanisms

Table 1: Pharmacological activities exhibited by various nutraceuticals

Nutraceuticals and dose	Animal model	Duration of therapy	Pharmacological activity	Reference
Aged garlic extract (250 mg kg^{-1})	Doxorubicin induced wistar albino male rats	27 days	Antioxidant activity	Alkreathy *et al.* (2010)
Garlic (250 and 500 mg kg^{-1})	Isoproterenol induced male swiss albino mice	30 days	Cardioprotection by promoting NO signalling pathway	Khatua *et al.* (2012)
Ginger (25 mg kg^{-1})	Streptozotocin+cholesterol fed diet induced diabietes in sprague-dawley male rats	42 days	Antioxidant, Anti-atherogenic activity	Al-Azhary (2011)
Ginger (500 mg kg^{-1})	High fat diet administered Wistar albino male rats	42 days	Antihypertensive Antidyslipidemic activity	Sanghal *et al.* (2012)
Ginger (200 mg kg^{-1})	Isoproterenol induced wistar rats	20 days	Antioxidant, increase level of serum marker enzymes	Ansari *et al.* (2006)
Amla (10 or 40 mg kg^{-1})	Aging process in male wistar rats	100 days of 2 month aged rats	Antioxidant property, Anti-dyslipidaemia	Yokozawa *et al.* (2007)
Coriander (500 mg kg^{-1})	High cholesterol fed rabbits	120 days	Antioxidant property, lipid lowering property	Joshi *et al.* (2012b)
Methanolic extract of *Coriander sativum* seeds (100, 200 or 300 mg kg^{-1})	Isoproterenol induced male wistar rats	30 days	Antioxidant Inhibits myofibrillar damage	Patel *et al.* (2012)
Coriander sativum (20mg kg^{-1})	Hypercaloric diet fed meriones shawi rats	30 days	Hypoglycemic and hypolipidemic activity	Aissaouia *et al.* (2011)
Curcumin (75 mg kg^{-1})	Mice (*In vivo*)	4 weeks	Anti-inflammatory	
	Neonatal rat ventricular myocytes cultured cells(*In Vitro*)		Anti-fibrotic; inhibition of p300-HAT signalling	Li *et al.* (2009)
Black pepper (250 and 500 mg kg^{-1})	Adriamycin induced model in wistar rats	21 days	Antioxidant property	Wakade *et al.* (2008)
Crocin (5, 10 and 20 mg kg^{-1} day^{-1})	Isoproterenol induced male Wistar albino rats	21 days	Antioxidant activity	Goyal *et al.* (2010)
Crocin (50 mg kg^{-1})	Diazinon induced male wistar rats	28 days	Alleviate apoptosis by reducing lipid peroxidation	Razavi *et al.* (2013)

Ginger: Ginger, a rhizome of plant *Zingiber officinale*, belonging to family Zingiberaceae, consumed as a spice in world cuisine (Khatua *et al*., 2012). Pharmacological activities exhibited by ginger are anti-emetic, anti-thrombotic, anti-microbial, anti-cancer, antioxidant and anti-inflammatory (Morakinyo *et al*., 2011; Ali *et al*., 2008). Ginger is beneficial in various diseases like arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and helminthiasis (Afzal *et al*., 2001). Phytoconstituents present in ginger are phenolic compounds such as shogaols and gingerols; terpins and sesquiterpenes, galanolactone, gingesulfonic acid, zingerone, geraniol, neral, mono acyldigalactosyl glycerols, ginger glycolipids (Kemper, 1999). Gingerol act as cardioprotectant by relaxing blood vessels and stimulating blood flow (Vasanthi and Parameswari, 2010). Evidences showed that ginger elicits its cardioprotective effects due to its important phytoconstituents. Gingerol inhibit thromboxane formation as well as gingerols and shogaols attribute the potent anti-platelet aggregation through the blockade of COX and Lipo-oxygenase (LOX) pathway *in vitro* (Srivastava, 1986; Guh *et al*., 1995) (Fig. 2). Polyphenolic flavonoids present in ginger contributes to anti-atherosclerotic activity in coronary artery by reducing platelet aggregation, reducing damage from ischemia and reperfusion, reducing plasma cholesterol levels and by inhibiting LDL oxidation (Van Jaarsveld *et al*., 1996; Aviram and Fuhrman, 1998). Altered fibrinolytic state due to fatty food has also been neutralized by ginger (Verma and Bordia, 2001). Ginger reduces the clumping of blood platelets, where no alteration has been found in blood lipid and sugar levels and fibrinogen activities of the coronary artery patients (Weiner, 1994; Bordia *et al*., 1997) (Fig. 2). Supplementation of food with aqueous and ethanolic extract of ginger significantly showed antioxidant effects by scavenging free radicals and by modulating the antioxidant of SOD and catalase enzymatic activity (Morakinyo *et al*., 2011) (Fig. 2). Furthermore, reduction of malondialdehyde (MDA) level also confirmed the antioxidant effect of Ginger (Stadtman, 2004). Ginger exhibits the potent anti-inflammatory activity by inhibiting endogenous prostaglandins through COX inhibition and by reducing the inflammatory mediated pathway (Weiner, 1994). Ginger produced a decline in blood glucose and significant decrease of triglyceride levels as well as significant reduction in malondialdehyde concentration and elevation in total plasma antioxidant activity. Further, ginger ameliorated the cellular changes of aortic wall induced in diabetic cholesterol-fed animals showing its anti atherogenic effect which could be beneficial for cardioprotection (Al-Azhary, 2011). Ginger

is effective in preventing hypertension and hyperlipidemia, the two most important risk factors associated with high incidence of myocardial infarctions. It reduces systolic blood pressure as well as high cholesterol levels significantly at the dose of 250 mg kg^{-1}, when compared to control and garlic fed group (Sanghal *et al*., 2012). Ginger also shows cardioprotection in isoproterenol induced myocardial infarction through attenuating serum Lactate dehydrogenase (LDH), Aspartate transaminase (AST), Alanine transaminase (ALT), Creatine kinase (CK) levels. It also attributes antioxidant, hypolipidemic, hypoglycemic and inhibits platelet aggregation activity (Ansari *et al*., 2006) (Table 1).

***Phyllanthus emblica*/Amla:** *Phyllanthus Emblica* (Amla) or Indian gooseberry, a fruit obtained from *Embelica officinalis* (EO), medium to large deciduous tree belonging to family Euphorbiaceae is native to India, Sri Lanka, Pakistan, Uzbekistan and China (Khan, 2009). Pharmacological actions exhibited by amla fruit are immunomodulatory, antioxidant, anti-pyretic, analgesic, cytoprotective, anti-tussive and gastro protective. It has also potent memory enhancing and cholesterol lowering effects (Khan, 2009). Blended with other fruits or alone, it is a rich source of vitamin C which exhibit non-enzymatic antioxidant defense mechanism. Vitamin C in EO accounts for approximately 45-70% for its antioxidant activity (Scartezzini *et al*., 2006). Active chemical constituents of EO are gallic acid, ellagic acid, 1-O-galloyl-beta-D-glucose, 3, 6-di-O-galloyl-Dglucose, chebulinic acid, quercetin, chebulagic acid, corilagin, 1, 6-di-O - galloyl beta D glucose, 3-Ethyl-gallic acid and isostrictiniin (Zhang *et al*., 2003). Emblica officinalis show potent antioxidant activity by inhibiting lipid peroxidation level and elevating antioxidant SOD, catalase and glutathione enzyme levels (Esterbauer *et al*., 1991) (Fig. 2). Amla extracts also decrease oxidative stress and scavenge free radicals resulting reduced blood sugar level in diabetic control animals (Sabu and Kuttan, 2002). It is one of natural compound gives potent anti-atherosclerotic activity as well as reduced total cholesterol and LDL levels in animal experimental studies (Kumar and Muller 1999; Saravanan *et al*., 2007) (Fig. 2). Moreover, amla extracts inhibit production of advanced glycation end products Aged Garlic Extract (AGEs) damaged, "sugar-coated" proteins that contribute to endothelial dysfunction and atherosclerosis (Ramasamy *et al*., 2008; Gao *et al*., 2008). It also reduces both serum and tissue lipid levels which similar to those of the "statin" drugs without adverse effects (Anila and Vijayalakshmi, 2002; Antony *et al*., 2006). Amla prevents inflammatory blood cells from "sticking" to endothelial linings, the first step in the production of atherosclerosis and subsequently prevents free radicals mediated thickening of vessel walls (Duan *et al*., 2005; Cai, 2006). Amla increases hepatic PPAR-α protein level which regulate the transcription of genes involved in lipid and cholesterol metabolism. Amla also decreases the elevated level of oxidative stress marker TBARS and pro-apoptotic proteins bax. Further, it increases anti-apoptotic protein bcl-2 level which protects against cell death by acute oxidative stress. Amla extract reduces the iNOS and COX-2 expression levels by inhibiting NF-kB activation in aged rats thereby showing its anti-inflammatory action (Yokozawa *et al*., 2007) (Table 1).

***Coriandrum sativum*:** *Coriandrum sativum* L., an annual herb of the parsley family Apiaceae, grown widely as a spice all over the world. Active constituents of coriander seed oil are α-pinene, limonene, β-phellandrene, eucalyptol, linalool, borneol, β-caryophyllene, citronegeraniol, thymol, linalylacetate, geranyl acetate, caryophyllene oxide and elemoland methyl heptenol (Bhuiyan and Fukunaga, 2009). Coriander leaf oil contains mainly aromatic acids viz., 2-decenoic acid, E-11-tetradecenoic acid, capric acid, undecyl alcohol, tridecanoic acid and undecanoic acid. Coriander oil is widely useful as carminative, spasmolytic, digestive and galactagogue; used in lotions and shampoos. Along with castor oil it is useful in rheumatism (Asolkar *et al*., 1992; Chopra *et al*., 1956; Ghani, 2003; Yusuf *et al*., 1994). *Coriandrum sativum* also attributes antimicrobial, antianxiety, analgesic, anticonvulsant, antifertility, antiasthamatic and insulin like activities (Joshi *et al*., 2012b). Coriander seeds give hypolipidemic action by decreasing cholesterol and triglycerides levels (Vasanthi and Parameswari, 2010) (Fig. 2). *Coriandrum sativum* reduced dyslipidemia associated complications by quenching free radicals generation in the body as a result of high fat diet (Lin *et al*., 2004). Oral administration of coriander sativum decreased the level of total cholesterol, triglyceride, phospholipids, LDL and Very Low Density Lipoprotein (VLDL), as well as increase High Density Lipoprotein (HDL) level. Decreased cholesterol levels maintained by *Coriandrum sativum* are mediated by increased LDL receptor activity (Lin *et al*., 2004; Suneetha and Krishnakantha, 2005). It also exhibit potent antioxidant activity by increasing catalase, glutathione and SOD and by decreasing lipid peroxidation. Flavonoids present in coriander oxidize free radicals by donating hydrogen atoms (Joshi *et al*., 2012a) (Fig. 2). *Coriandrum sativum* enhances the enzymatic activity of catalase, a major part of antioxidant defense mechanism. Moreover, glutathione levels increased by coriander juice show its potent antioxidant effect for mitochondria against endogenously generated oxygen radicals (Joshi *et al*., 2012a). GSH

content and catalase activities have been increased after the treatment with 70% methanolic extract of *Coriandrum sativum* (Lin *et al*., 2004). In the lumen of arteries, there is a vulnerable plaque formation caused by platelet aggregation due to impairment in the supply of blood to cardiac tissue. The leaf spices extract of *Coriandrum sativum* imparts anti-platelet aggregation activity due to presence of high concentration of natural antioxidants. In different concentration, aqueous extracts of coriander and curry leaf spices potentially inhibit the human platelet aggregation (Patel *et al*., 2012) (Fig. 2). Methanolic extract of *Coriandrum sativum* at the dose of 200 and 300 mg kg^{-1} prevented the isoproterenol induced increase in the serum levels of CK-MB, LDH, AST, ALT and uric acid. Further this is able to prevent myocardial infarction by inhibiting myofibrillar damage (Aissaouia *et al*., 2011) (Table 1). Single oral dose of CS-extract (20 mg kg^{-1}) reduced plasma glucose, insulin and Insulin resistance, total cholesterol, LDL-cholesterol and triglycerides in normal and Obese Hyperglycemic Hyperlipidemic (OHH) Meriones shawi rats suggesting its anti-atherosclerotic and cardioprotective effect (Nawaz *et al*., 2011) (Table 1).

Curcumin: Curcumin, a curry spice polyphenol isolated from the roots of *Curcuma longa* imparts yellow colour to turmeric (Kiuchi *et al*., 1993), belongs to family Zingiberaceae. Curcuminoids are the major ingredients present in the curcumin. Turmeric curcuminoids are demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin 3) and recently identified cyclocurcumin (Araujo and Leon, 2001). Long listed uses of curcumin include antioxidant, anti-inflammatory, anti-cancer, anti-malarial, insect repellant, antiseptic, analgesic and wound healing activities (Goel *et al*., 2008). Anti-inflammatory effects of curcumin prevent atrial arrhythmias, whereas correcting Ca^{2+} homeostasis by curcumin is useful in the prevention of ventricular arrhythmias (Shishodia *et al*., 2007). A large body of evidences suggests that curcumin has a diverse range of molecular targets including transcription factors, growth factors, cytokines, enzymes and genes regulating cell proliferation and apoptosis. Anti-inflammatory effect of curcumin is mostly mediated through inhibition of COX-2, LOX and iNOS. Curcumin attributes potent anti-inflammatory activity through down regulation of NF- κB, consequently decrease in the expression of TNF-α, IL-1 and IL-6 (Shishodia *et al*., 2007) (Fig. 2). Curcumin inhibit the independent Mitogen Activated Protein Kinase (MAPK) pathways which imparts a crucial role in the activation of inflammatory stimuli (Soni and Kuttan, 1992). Anti-atherosclerotic activity of curcumin is due to reduction in level of serum lipid peroxides and total serum cholesterol and increase in the serum HDL level (Shah *et al*., 1999) (Fig. 2). The inflammatory process plays a crucial role in the pathogenesis of many cardiovascular disorders such as atherosclerosis, acute coronary syndrome and atrial arrhythmias (Shishodia *et al*., 2007). Curcumin inhibit platelet aggregation mediated by the platelet agonist's Platelet-Activating Factor (PAF) and arachidonic acid in low concentration, whereas epinephrine, ADP and collagen agonists are inhibited by its high dose concentration (Yanazume *et al*., 2003). P300 is a critical Histone Acetyl Transferase (HAT) and its transcriptional activity is enhanced during agonist-induced cardiac hypertrophy (Li *et al*., 2009). Upregulation of p300-HAT promotes NF-κB (a marker of inflammation) and TGF-β1 (component which induce collagen synthesis) activation. Curcumin at the dose of 75 mg kg^{-1} day^{-1} for 4 weeks targets p300-HAT and attenuates cardiac hypertrophy *in vitro* and *in vivo*. Further curcumin also blocked aortic banding induced inflammation and fibrosis through disrupting p300-HAT-dependent signaling pathways (Jayaprakasha *et al*., 2003) (Table 1).

Cinnamon: Cinnamon belongs to genus Cinnamomum, family Lauraceae, distributed in India, Egypt, China, Srilanka and Australia. Cinnamon leaves and bark are extensively used as spices in food or to produce essential oils (Jakhetia *et al*., 2010). Cinnamon attributes antioxidant, anti-microbial, anti-diarrhoeal, anti-ulcer, hypolipidemic and hypoglycemic activities (Tung *et al*., 2008). The chemical constituents containing cinnamon are essential oils, resinous compounds, cinnamaldehyde and cinnamate. Essential oil contains trans-cinnamaldehyde, caryophyllene oxide, L-borneol, L-bornyl acetate, eugenol, b-caryophyllene, E-nerolidol and cinnamyl acetate (Singh *et al*., 2007). Cinnamaldehyde is responsible for pungent taste and scent; other chemical constituents are Terpinolene, α-Terpineol, α-Cubebene and α-Thujene (Shahidi *et al*., 1992). Cinnamon like antioxidants is added into food to prevent free radical chain reaction, inhibiting the initiation and propagation step leading to terminate the reaction and delay oxidation process (Mathew and Abraham, 2006). It has been reported that methanolic extract of cinnamon contains number of antioxidant compounds, can effectively scavenge the ROS including superoxide anions and hydroxyl radicals under *in vitro* conditions (Kim *et al*., 2010) (Fig. 2). *Cinnamomum cassia* is a traditional medicine helpful in improvement of blood circulation responsible for prevention of myocardial infarction recently reported that its extracts exhibits anti-platelet aggregation and anti-coagulant properties (Hwa *et al*., 2012) (Fig. 2). Methoxy cinnamialdehyde (MCA) reduced the expression of High mobility group box 1 (HMGB1), an activator of the inflammatory cascade when released into

the extracellular space and VCAM-1 in I/R myocardium along with increase of Haem-oxygenase-1 (HO-1) induction. The reduced injury was accompanied by significantly reduction of neutrophils infiltration and increased SOD activity in ischemic tissues and reduced serum level of cardiac cTnI. MCA significantly inhibited NF-κB luciferase activity in TNF--activated endothelial cells. As expected, 2-MCA significantly inhibited monocyte (U937) adhesion to endothelial cells (Kim *et al*., 2009; Vijayan and Thampuran, 2000; Chandrasekar and Freeman, 1997; Gurevitch *et al*., 1996). Cinnamon may prevent myocardial infarction like complications such as oxidative stress mediated free radicals and high lipid level through antioxidant defense mechanism and its hypolipidemic activity.

Black pepper: Black pepper is a flowering vein, obtained from *Piper nigrum*, belongs to family Piperaceae, used as spice native to South India. *Piper nigrum* roots gives pellitorine, (E)-1-[3', 4'-(methylenedioxy) cinnamoyl] piperidine, 2, 4-tetradecadienoic acid isobutyl amide, piperine, sylvamide, cepharadione A, piperolactam D and paprazine (Vasanthi and Parameswari, 2010). Black Pepper attributes antioxidant and anti-bacterial activities and helps in digestion and weight loss through breakdown of adipose tissue. Black pepper actually maintains and enhances the levels and efficacy of important antioxidant compounds. It contains several powerful antioxidants and is thus one of the most important spices for preventing and curtailing oxidative stress. Therefore, black pepper is called as a source of effective antioxidant (Vasanthi and Parameswari, 2010; Meghwal and Goswami, 2012; Bhuiyan and Fukunaga, 2009) (Fig. 2). Piperine demonstrated as to protect against oxidative damage by inhibiting free radical and ROS. Furthermore, hypolipidemic effect shown by piperine is due to decreasing cholesterol, free fatty acids, phospholipids and triglycerides levels in high fat diet rats (Vasanthi and Parameswari, 2010) (Fig. 2). Piperine also attributes potent anti-inflammatory action through inhibit the production of proinflammatory mediators; IL-6, PGE_2 and IL-1β. Black pepper is also rich in vanadium which promotes cardiac function by activating Akt signaling through inhibition of tyrosine protein phosphatase (Vijayakumar *et al*., 2002). Supplementation of black pepper in high fat diet rats elevates the level of HDL and reduces the level of LDL and VLDL when compare with unsupplemented high fat rats (Wakade *et al*., 2008). Methanolic extract of fruits of *Piper longum* attributes cardioprotection in adriamicin induced cardiotoxicity by virtue of its antioxidant property. Treatment with 250 and 500 mg kg^{-1} of *Piper longum* extracts for 21 days ameliorates the effect of adriamicin on lipid peroxidation and restores the activities of marker enzymes AST, ALT, LDH and CK in heart with a concomitant increase in their activities in serum. Further lowered activities of myocardial antioxidant enzymes like catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase along with reduced glutathione were significantly increased by *Piper longum* (Gupta *et al*., 2008) (Table 1).

***Cinnamomum tamala*:** *Cinnamomum tamala,* a spice belonging to family Lauraceae, is widely native to tropical and sub-tropical Asia, Australia, Pacific region and South America (Megraj *et al*., 2011). *Cinnamomum tamala* attributes hypolipidemic effects, anti-diabetic, antioxidant, anti-ulcer, anti-inflammatory, hepatoprotective, anti-diarrhoeal, immunosuppressive and anti-bacterial activities (Kar *et al*., 2003). In some formulation *Cinnamomum tamala* is patented as anti-diabetic and antidote for tobacco. It has also been used as an astringent, stimulant, carminative and diuretic and in cardiac disorders as traditional medicine (Mir *et al*., 2004). Phytochemical studies evidence the presence of eugenol, β-caryophyllene and linalool, trans-sabinene hydrate, (Z)-β-ocimene, myrcene, α-pinene and β-sabinene, germacrene A and α-gurjunene (Kumar *et al*., 2012; Dighe *et al*., 2005). *Cinnamomum tamala* leaf oil contains various chemical constituents; eugenol, the main component followed by spathulenol, viridiflorene, methyleugenol, aromadenendrene with other constituents in minor amounts[112]. It attributes anti-inflammatory action through membrane stabilizing activity (Dhulasavant *et al*., 2010) (Fig. 2). *Cinnamomum tamala* shows potent antioxidant activity by scavenging superoxide and hydroxyl radicals in a concentration dependent manner (Dhulasavant *et al*., 2010). *Cinnamomum tamala* aqueous and ethanolic leaf extracts shows hypolipidemic action in high fat diet rats by preventing rise in serum levels of total cholesterol, triglyceride, LDL, VLDL and atherogenic index, whereas significant increases in the level of HDL has been observed (Dwivedi, 2007) (Fig. 2).

***Terminalia arjuna*:** *Terminalia arjuna* is the bark belonging to family Combretaceae and is commonly called hridya. Tree bark powder of *Terminalia arjuna* is composed of flavonoids, tannins, minerals, oleanane triterpenoids (arjunolic acid), arjunic acid, glycosides (arjunetin arjunosides I, II, III, IV), gallic acid, ellagic acid, oligomeric proanthocyanidins and phytosterols (Oberoi *et al*., 2011; Dwivedi and Agarwal, 1994). Pharmacological activities have been attributed due to flavonoids worked as antioxidant, anti-inflammatory, antihyperlipidemic and antihypercholestrolemic. Whereas, presence of glycosides exhibits cardioprotective activity through antioxidant mechanism.

Terminalia arjuna is a cardiotonic and exhibits positive ionotropic effect through release of nor-epinephrine from sympathetic nerve ending in arterial muscles as well as, enhanced coronary blood flow by release of PGE_2, beneficial for Coronary Artery Disease (CAD) patients (Altaf *et al*., 2012; Dwivedi and Jauhari, 1997). It also exhibits anti-thrombotic activity by inhibiting phosphoinositol-phospholipase-C and also shows anti-platelet activity by inhibiting the formation of diacylglycerol and inositol triphosphate in CAD (Urizar and Moore, 2003) (Fig. 2).

Commiphora mukul: *Commiphora mukul* (guggul) an oleo-gum resin obtained from mukul myrrh tree belongs to family Burseraceae. It is a traditional medicine in India for the last 2000 years and beneficial in diseases including rheumatism and hyperlipidemic disorders (Francis *et al*., 2004; Urizar and Moore, 2003). *Commiphora mukul* extract in traditional formulations has been used as treatment for inflammation, obesity and lipid disorders (Gaur *et al*., 1997). *Commiphora mukul* exhibits fibrinolytic activity consequently by decreasing platelet adhesion and scavenging of free radicals in atherosclerotic ischemic patients further reduce cellular damage from ischemia (Mary *et al*., 2003; Mahmood *et al*., 2010). Moreover, due to presence of guggulsterones in ethyl acetate extract, plant exhibits cardioprotective properties by decreasing the concentration of blood LDL level by enhancing uptake of LDL by liver (Ojha *et al*., 2008). However, guggulsterones stereoisomers of *Commiphora mukul* are responsible for anti-hyperlipidaemic action (SuryaPrakash *et al*., 2012) (Fig. 2).

Terminalia chebula: *Teminalia chebula*, a moderate tree used in traditional medicines belongs to family Combretaceae. Main Chemical constituents are triterpenes arjun glucoside-1, arjungenin and the chebulosides-1 and 2 and other constituents contains tannins, chebulic acid, chebulinic acid, ellagic acid, 2, 4-chebulyi–β-D-gluco pyranose, gallic acid, ethyl gallate, punicalagin terflavin A , terchebin, some purgative as anthraquinone, flavonoids like luteolin, rutins and quercetin etc. (Zia-Ul-Haq *et al*., 2012). Pharmacological activities contributed by *Terminalia chebula* are anti-cancer, immunosuppression, hepatoprotective, cardioprotective, radioprotective, anti-diabetic, renoprotective, anti-HIV, purgative, antioxidant, antiaging, antiulcer, helicobacter pylori, antityphoid, anticaries, wound healing and increasing gastric emptying (Kar *et al*., 2003). It's also worked as herbal supplement for blood clotting associated diseases (Suchalatha and Shyamala, 2004). *Terminalia chebula* ameliorates the lipid peroxides formation in isoproterenol induced myocardial infarction. It also attributes anti-platelet aggregation property in concentration dose dependant manner (Suchalatha and Shyamala, 2004). *Terminalia chebula* exhibits cardioprotective activity through antioxidant mechanism by decreasing activity of myocardial marker enzymes with a concomitant increase in their activity in serum (Yuan *et al*., 2008) (Fig. 2).

Salvia miltiorrhiza: *Salvia miltiorrhiza* is used in Chinese medicines for treating vascular diseases belongs to family Lamiaceae. It is beneficial in diseases like liver fibrosis, cirrhosis, central nervous system diseases, hypertension, angina pectoris, myocardial infarction, stroke, ischemia, hyperlipidemia, hepatitis, miscarriage, diabetes, arrhythmia and myocardial ischemic injury (Wang *et al*., 2002; Zhang and Chen, 1994). It shows antioxidant activity by decreasing lipid peroxides and significantly increasing the activities of anti-oxidant defense enzymes like SOD, catalase and glutathione peroxidase (Zhang and Chen, 1994) (Fig. 2). *Salvia miltiorrhiza* inhibits platelet aggregation, reduced blood viscosity as well as improved myocardial ischemia (Xing *et al*., 1996). Due to potent antioxidant action it prevents the oxidation of LDL (Karmin *et al*., 2001). Moreover, it also increases the production of nitric oxide which is vasodilator and promotes blood flow (Karmin *et al*., 2000) (Fig. 2). It also exhibits cardioprotective action after heart attack, is beneficial after balloon angioplasty and also protects the patient with cardiovascular diseases during surgery (Zhou *et al*., 1999; Zhang *et al*., 1998; Ji *et al*., 2003).

Walnut: Walnut, (*Juglan regia*) belonging to family Juglandaceae are very good source of Mg^{2+} and Cu^{2+}, cofactors for number of enzymes of antioxidant defense mechanism (Anderson *et al*., 2001). It contains ellagic acid as antioxidant, protects healthy cell from free radical damaging and prevents cancer causing cells replication. Due to presence of omega-3, it attributes cardioprotective activity by preventing cardiac arrhythmia and blood clot formation into arteries, increase HDL concentration and decreased LDL level (Palanisamy *et al*., 2011). Nuts exhibit cardioprotective effect but these are avoided in the fear of weight gain due to presence of fatty acids and nutrients (Palanisamy *et al*., 2011). Moreover, it also shows anti-hypertensive and anti-inflammatory activity. Enhancement in endothelium dependant vasodilation and reduction in vascular adhesion level by walnut consequently inhibits inflammatory cytokines (Constance and Nela, 2008) (Fig. 2).

Saffron: Saffron, the dried stigmas of *Crocus sativus* L., a member of Iridaceae family and a traditional spice that has good flavour and red color is one such make it a popular plant. *Crocus sativus* is widely used to promote

health and fight against diseases. Saffron extracts consists of most important bioactive constituents such as crocetin, picrocrocin (precursor of safranal) and crocin (glycosyl esters of crocetin, belongs to caretonids), are responsible for characteristic color of saffron. Safranal (a volatile compound) is another active ingredient, accounts for special odour and golden yellow colour occurrence due to presense of crocin pigments (Bhargava, 2011). It has been shown that saffron possesses antioxidant (Joukar *et al*., 2010; Hosseinzadeh *et al*., 2009; Hosseinzadeh and Shariaty, 2007), anticarcinogenic (Aung *et al*., 2007; Dhar *et al*., 2009), anti-inflammatory (Hosseinzadeh and Younesi, 2002) and immunomodulating property (Das *et al*., 2004) (Table 1). The active ingredients behind these effects have been identified as crocin and crocetin. Cardioprotective effects of saffron in experimentally induced myocardial necrotic rats are reduced myocardial contractility and oxygen demand and increased adenosine triphosphate storage (Grimm *et al*., 1998) (Fig. 2). In isoproterenol induced cardiotoxicity, disturbed redox status and lipid peroxidation was significantly improved by crocin, a carotenoid pigment of saffron. A marked reduction in the activities of myocardial creatine kinase-MB (CK-MB) isoenzyme, lactate dehydrogenase (LDH), superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) levels along with an increase in content of melondialdehyde (MDA) were observed with 20 mg kg^{-1} dose of crocin. Crocin also improved left ventricular function by increasing inotropic. (+LVdp/dt, marker of myocardial contraction) and lusitropic (-LVdp/dt, marker of myocardial relaxation) states of the heart. Further cardioprotective effect of crocin was reconfirmed by histopathological and ultrastructural examinations (Goyal *et al*., 2010) (Table 1). Razavi *et al*. (2013) demonstrated in their study that crocin is effective against subchronic diazinon (DZN) induced cardiotoxicity in rats. Crocin (25 and 50 mg kg^{-1}) improved histopathological damages, decreased MDA and CK-MB, increased GSH content and attenuated the increase of Bax/44 Bcl2 ratio, activation of caspase 3 and release of cytochrome c to the cytosol induced by DZN (Table 1).

***Ocimum sanctum*:** Plants are the important sources of medicines. *Ocimum* species belonging to family Lamiaceae have high therapeutic potential (Das and Vasudevan, 2006). *Ocimum sanctum* L. (Tulsi, the holy basil) is also named as "The Incomparable One", "The Mother Medicine of Nature" and "The Queen of Herbs" is surplus with active chemical constituents Eugenol (70%) Carvacrol (3%), Eugenol methyl ether (20%) Caryophyllin, linalool, Aneole, Chavicol, nerol, terpinin 4-01, decylaldehyde, r-selinene, α and β-pinenes, champhor sesequiterpenes, volatile oils, alkaloids, glycosides, saponins and tannins (Joshi *et al*., 2012a). Eugenol is main contributor to the therapeutic potential of Tulsi. *Ocimum sanctum* contributed antifertility, anticancer, antidiabetic, antifungal, antimicrobial, hepatoprotective, cardioprotective, antiemetic, antispasmodic, analgesic, adaptogenic and diaphoretic actions (Pattanayak *et al*., 2010). Aqueous extract of *Oscimum sanctum* enhances the activity of SOD, catalase antioxidant enzymes (Gupta *et al*., 2006) (Fig. 2). Aqueous extract of *Oscimum sanctum* inhibits the hypercholesterolemia-induced erythrocyte lipid peroxidation activity, decreasing the serum cholesterol, triacylglycerol, LDL and VLDL cholesterol in male albino rabbits (Joshi *et al*., 2012a; Geetha and Vasudevan, 2004) (Fig. 2). Civsilineol, Civsimavatine, Isothymonin, Apigenin, Rosavinic acid and Eugenol important active constituents present in *Oscimum sanctum* extract attribute anti-inflammatory activity by inhibiting COX activity (Joshi *et al*., 2012a; Kelm *et al*., 2000). Intrarenous avenous infusion of *Oscimum sanctum* oil exihibits hypotensive effect by vasodilation and inhibit the formation of series of PGEs 1, 2, 3 (Singh *et al*., 2001). *Oscimum sanctum* oil, cardioprotective in isoproterenol induced myocardial necrosis by endogenous antioxidant defense mechanism (Sood *et al*., 2005).

Vitamin D: Vitamin D (fat soluble vitamin) present in minor foods and formed endogenously in the existence of ultraviolet light obtained from sunlight. D_2 (ergocalciferol) and D_3 (cholecalciferol) are the two main types of Vitamin D (Liss and Frishman, 2012). Foods containing D_3 are cod liver oil, salmon, mackerel and tuna. Vitamin D receptors are present in every tissue including cardiomyocytes and Vascular Smooth Muscle Cells (VSMCs) (Mitsuhashi *et al*., 1991; Simpson and Weishaar, 1988). Experimental evidences proved that vitamin-D reduced levels or deficiency lead to coronary artery diseases, congestive heart failure, hypertension, endothelial cell dysfunction, vascular and myocardial cell calcification and increased inflammation (Liss and Frishman, 2012; Davies and Hruska, 2001; Schurgers *et al*., 2001; Canning *et al*., 2001; Muller *et al*., 1992). Zittermann *et al*. (2008) showed that inadequate vitamin D leads to low levels of calcitrol which effect several mechanisms involved in vascular smooth muscle proliferation, myocardial calcification, increased inflammatory processes and heart attack thereby contributing to cardiovascular disorders (Zittermann *et al*., 2008) (Fig. 3).

Vitamin-C: Vitamin-C is an antioxidant vitamin obtained from fresh broccoli, green and red peppers, collard greens, brussel sprouts, cauliflower, lemon,

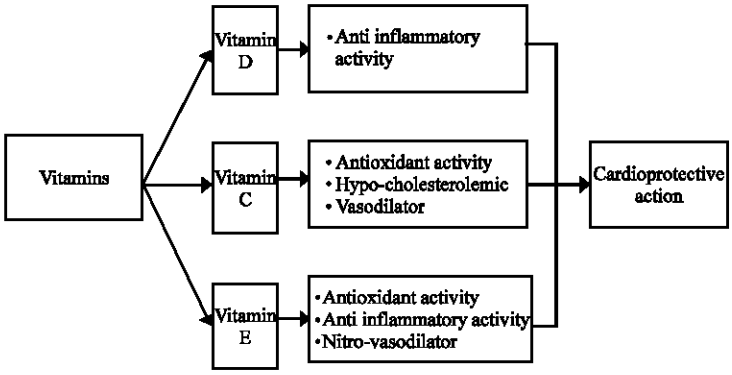

Fig. 3: Cardioprotective action of vitamins

cabbage and pineapples, strawberries and citrus fruits. Intake of high vitamin-C is inversely proportional to occurrence of coronary heart diseases (Enstrom *et al*., 1992). Vitamin-C exhibits antioxidant activity by scavenging free radicals such as molecular oxygen, superoxide, hydroxyl radical and hypochlorous acid (Padayatty and Levine, 2000). Vitamin-C is strong antioxidant in human blood plasma and inhibits the oxidation of LDL (Frei, 1991; Jialal and Grundy, 1991; Frei *et al*., 1990; Harats *et al*., 1990; Frei *et al*., 1989). Ascorbate prevents the initiation of lipid peroxidation by donating electrons (Padayatty and Levine, 2000; Frei, 1991; Frei *et al*., 1990). Vitamin-C also reduces cholesterol level and improves vasodilation and vascular activity (Padayatty and Levine, 2000; Bassenge *et al*., 1998; Carr and Frei, 1999). Raised blood pressure in normotensive and hypertensive men is due to deficiency or lowered level of vitamin-C in plasma (Salonen *et al*., 1988). High dose of vitamin-C are reported to induce vasodilation in coronary arteries (Bassenge *et al*., 1998; Carr and Frei, 1999) (Fig. 3). In Clinical studies Riemersma *et al*., determine that low plasma vitamin C concentrations conferred a risk of angina in population (Riemersma *et al*., 2000). Thus, vitamin-C is an essential supplement for the prevention of the myocardial infarction.

Vitamin-E: Vitamin-E is a lipid soluble antioxidant in human plasma and lipoprotein. Vitamin-E is mostly used in food supplements and cosmetic products. Absorption of vitamin-E is inversely proportional to development of coronary artery diseases in human beings (Wong and Lodge, 2012; Stocker, 1999). Vitamin-E reduces the oxidative stress and inflammation (Devaraj *et al*., 2007). Vitamin-E inhibits the oxidative modification of LDL and thus, inhibits the promotion of atherosclerosis (Munteanu *et al*., 2004). Vitamin-E attributes cardioprotection as well as influence number of biological and metabolic functions through inhibition of protein kinase C, activating diacylglycerol kinase and protein phosphatase 2A and regulating specific gene expression (Rimbach *et al*., 2010; Azzi *et al*., 2000, 2004). Vitamin-E also inhibits the platelet aggregation independent of its antioxidant activity (Freedman and Keaney, 2001). *In vitro* and *in vivo* PKC, arachidonic acid and phorbol ester dependent platelet aggregation is successfully reversed by vitamin E (Freedman *et al*., 1996). Vitamin-E is also helpful in maintaining vascular homeostasis by increasing eNOS mediated NO production (Diaz *et al*., 1997) (Fig. 3).

CONCLUSION

Patients with hypertension, atherosclerosis and diabetes mellitus are major risk of myocardial infarction. Thus, dietary supplements that can modulate myocardial infarction and potentially improve lipid parameters, oxidative stress, inflammation, would be desirable. Herbal medicine lost ground to the new synthetic medicines. But now days, they are gaining greater acceptance from the public and the medical profession due to greater advances in understanding the mechanism of action by which herbs can positively influence health and quality. Moreover patients suffering from abnormalities which could lead to infarction could benefit from a low-risk, inexpensive, food-based intervention aimed at normalizing their metabolic milieu. Data of spices, fruits, nuts and vitamins presented in this review suggested that these nutraceuticals hold promise as preventive interventions for myocardial infarction.

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