A Review on Protective Role of Phytoconstituents Against Isoproterenol Induced Myocardial Necrosis


Department of pharmaceutical chemistry, GITAM Institute of Pharmacy, GITAM University, Andhrapradesh

Available Online: 1st May, 2016

ABSTRACT

Heart disease remains the principal cause of death claiming millions of lives every year. Owing to technology and changes in life style the myth of myocardial infarction primarily affecting elderly people has been busted with heart disease claiming significant number of lives among young people also. Myocardial infarction occurs when a section of the heart is deprived of oxygen leading to necrosis of the tissue. Isoproterenol induced myocardial necrosis came to light during the late fifties. Conventional drugs are likely to reduce mortality, but their general applicability is limited by problems with toxicity and cost. Herbal medicine is used by more than one-fifth of the global population and it is an adept alternate to synthetic drugs. The objective of current review is to assess the cardio protective potential of phyto constituents like alkaloids, organo sulphur, carotenoids, flavonoids, glycosides, terpenoids, saponins and phenolic acid against isoproterenol induced myocardial necrosis in rats. Pretreatment of rats with these phytoconstituents significantly prevented the deviated biochemical variations such as marker enzymes, lipid profile and antioxidant parameters to near normal status. This review article provides a comprehensive account of structure, dose and medical efficacy of cardio protective phytoconstituents.

Keywords: Cardioprotection, Isoproterenol, Myocardial infarction, Myocardial necrosis, Phytoconstituents.

INTRODUCTION

Human heart is a vital organ without which survival is next to impossible. According to world health organisation data 16.7 million people die each year due to myocardial infarction¹. Myocardial infarction occurs when there is a significant reduction or block in the blood supply to the heart, leading to degeneration of a portion of the myocardium. Necrosis of myocytes is the pathological indication of myocardial infarction. Risk factors of myocardial necrosis include diabetes, high blood pressure, hypercholesterolemia, smoking, gender, age and sedentary lifestyle².

Myocardial necrosis

During commonly encountered injuries like ischemia, exposure to toxins, physical agents, chemical agents, various infections, trauma etc the cell chooses necrosis as the common pathway to cell death³. When myocytes are exposed to these kinds of inherently damaging agents, it culminates in cell death. The infarcted myocardium begins to undergo coagulative necrosis between 4 and 12 h after cell death. Morphological changes associated with necrosis are loss of total nuclei, cytoplasmic cross-striations and neutrophilic infiltration in first three days, myocyte fragmentation in the first week and early phagocytosis after the first week. In the second week the granulation tissue progresses and evolves through progressively dense collagen deposition and a scar is completed by the second month⁴.

Isoproterenol induced myocardial necrosis

Soaring physical and mental stress can also root to myocardial infarction and unexpected demise, supporting a role for rise in catecholamines in myocardial infarction pathophysiology⁵. Isoproterenol is a synthetic catecholamine that has positive inotropic and chronotropic effect. At therapeutic doses it increases cardiac output, however when administered in large doses it was reported to cause severe oxidative stress in the myocardium leading to necrosis of the left ventricular heart muscle⁶. Isoproterenol generates free radicals by the process of autooxidation and this free radical mediated oxidative stress was believed to be the mechanistic pathway via which isoproterenol induced necrosis⁷. Free radicals initiate and propagate a chain of reactions that attack double bonds in membrane phospholipids yielding lipid peroxidation products like malondialdehyde and isoprostanones. When amino acids or proteins present in enzymes are subjected to sulfhydryl mediated cross-linking they undergo degeneration and lose their enzymatic activity. Such a process is mediated by free radicals leading to damage in mitochondrial membranes. This consequently results in decreased synthesis of adenosine tri phosphate (ATP). Deprivation of adenosine tri phosphate in cells causes failure of membrane bound ion pumps leading to cell swelling, and influx of calcium, depletion of glycogen stores and reduction in protein synthesis. Increased cytosolic calcium activates a series of enzymes, like phospholipases mediated membrane damage, endonucleases mediated chromatin...
fragmentation, and decrease in adenosine triphosphatases\(^8\). Free radicals stimulated the binding of tumor necrosis factor (TNF\(_R1\)) with death domain of receptor-interacting protein causing cell necrosis\(^9\). Concisely, free radicals induced myocardial necrosis resulted in damage of mitochondria, cellular membranes, DNA, disturbance in calcium homeostasis and misfolding of proteins\(^3\). The most relevant mechanisms by which isoproterenol causes myocardial necrosis are shown in Graphical abstract 1.

Diagnostic tools of myocardial necrosis are (i) changes in the electrocardiogram (ii) elevated serum enzymes such as creatine phosphokinase(iii) elevated cardiac proteins like troponin T or I (iv) decrease in antioxidant enzyme levels and (v) pain similar to that of angina\(^10\). Conventional treatment includes use of synthetic drugs like beta blockers, anticoagulants, antithrombolytics, ACE inhibitors and surgeries (cardiac catheterization, angioplasty). However these drugs are associated with limitations like side effects, cost, non availability, resistance development etc. Since herbal derived drugs are non toxic and eco friendly, these drugs must be given a deep approach. Herbal treatments have been used in people with congestive heart failure, renal failure and myocardial necrosis\(^11,12\). Several poly herbal and herbo mineral formulations are also useful in the treatment of myocardial necrosis. Some of the plants which possess myocardial activity are Allium sativum, Allium cepa, Curcuma longa, Asparagus racemosus, Caesalpinia bonducella, Cassia fistula, Emblica officinalis etc\(^13\). Literature survey showed as many as seventy phytoconstituents obtained from plants that are cardioprotective against isoproterenol induced myocardial necrosis. This review summarizes the chemistry of active metabolites and how they might fight against isoproterenol induced necrosis and highlights their potential as novel cardioprotectives. List of phytoconstituents, their dose and mechanism by which they protect biochemical parameters are given in Table1. The structure and IUPAC name of phytoconstituents are listed in Table 2.

**Phytoconstituents Proved to Be Protective Against Isoproterenol Induced Myocardial Necrosis**

**Alliin**

Alliin (S-allyl cysteine sulfoxide) is sulfur containing compound present in *Allium sativum* (garlic)\(^14\). It is composed of three units namely an allyl group, a sulfoxide group and the non essential amino acid cysteine. \(\gamma\)-glutamyl-S-allyl cysteine reacts with water molecules to produce alliin. Compounds like allyl thio sulfinate, allicin, allyl propenyl thiosulfinate, diallyl disulfide, and allyl methyl sulfide are synthesized from alliin\(^15\). Studies were carried out for the effective use of alliin in the treatment of potassium dichromate induced renal injury. It exhibited hypoglycemic effect by stimulating insulin production or interfering with dietary glucose absorption\(^16\). It also ameliorates the diabetic condition of alloxan treated rats. Alliin is a potent antimicrobial and antifungal agent. Alliin was evaluated for its preventive effect in isoproterenol induced myocardial ischemia. It exerted potent cardio protection by its anti oxidant and anti lipidaemic properties\(^17\).

**N-Acetyl cysteine (NAC)**

N-acetyl cysteine is a organo sulphur compound found in several vegetables, including garlic, shallots, bell pepper, onion and pepper. It is the acetylated form of the amino acid L-cysteine and essentially a prodrug that is converted to cysteine by the enzyme amino acylase and absorbed into the blood stream. The pharmacological activity of NAC is credited to its sulphydryl group\(^18\). It has potential as a chemopreventive agent\(^19\) and is the choice for the treatment of acetaminophen-induced hepatotoxicity\(^20\). It is being successfully used to treat a variety of neuropsychiatric and neurodegenerative disorders like Alzheimer’s and Parkinson’s diseases and in the treatment of human immune deficiency virus\(^21\). NAC stimulates gastro-pulmonary vagal reflex and ciliary muscles by which it clears the mucus from the airways. It inhibited isoproterenol stimulated inflammatory factors (TNF-\(\alpha\), IL-1\(\beta\)) thereby extending significant cardio-protective effect against ISO induced myocardial injury in rats\(^22\).

**Coptisine**

*Rhizoma coptidis* contains coptisine, which is an isoquinoline alkaloid. Other pharmacologically active alkaloids present in the plant are berberine, palmatine and epiiberberine\(^23\). It exhibited a wide variety of beneficial properties, including, anti-inflammatory, neuromodulatory and antimicrobial activities\(^24\). A high dosage of coptisine decreased the level of 3-Hydroxy-3-Methylglutaryl-CoA reductase enzyme suggesting a critical role in anti-hypercholesterolemia. Anti hepatoma and anti leukaemia actions of coptisine have also been reported. Most recently, studies showed that coptisine is a promising candidate for prevention or improvement of diabetic neuropathy and neuro degenerative disorders\(^25\). It attenuated mitochondrial respiratory dysfunction, suppresses expression of RhoA/ROCK (Rho-associatedcoiled-coil forming protein kinase, ROCK) and thereby exerted cardioprotective effect on isoproterenol induced myocardial infarction in rats\(^26\).

**Crocin**

Crocin is a natural carotenoid found in the flowers of *Crocus sativus L*, generally called as saffron (Iridaceae family). It has two ester groups formed from the sugar gentiobiose and the carboxylic acid crocetin. The color of saffron is mainly due to crocin. Among the other pharmacologically active constituents like picrocrocin and safranal of *Crocus sativus*, crocin is the most important and abundant antioxidant\(^27\). Crocin is water soluble xanthophylls and was reported to show antidepressant effect via the uptake inhibition of neurotransmitters\(^28\). In organic dye-sensitized solar cells studies speculate that it has the potential to be a good photosensitive agent. Research reveals crocin as potent antinoiceptive, antiinflammatory, hepatoprotective and anticancer agent\(^29\). A study showed that crocin has antioxidant effect in ischemia-reperfusion models of stroke. In addition, crocin exhibited cardioprotective effect in isoproterenol induced cardiac toxicity. It restored endogenous antioxidants and
lipid peroxides in such a way that maintained the redox status of the cell. Cinnamic acid and cinnamic aldehyde

Cinnamic aldehyde and its derivative cinnamic acid are the main chemical ingredients of Cinnamomum cassia. The existence of a disubstituted carbon-carbon double bond in the side chain of these chemicals gives rise to two different stereo isomers, referred to as the cis (Z) and trans (E) isomers. Experimental studies indicate that cinnamaldehyde possesses hypoglycemic and hypolipidemic effects in streptozotocin induced diabetic rats. Cinnamaldehyde has also shown anthelmintic, antiviral and gastrointestinal activities. Cinnamic acid possesses anti-tumor activity and reduces melanin production, likely via inhibition of tyrosinase. Cinnamic acid and cinnamaldehyde has been reported to have anti-oxidative, anti-inflammatory and anti-nephrotoxicity properties. Cinnamic acid and cinnamaldehyde reduced the serum levels of cardiac marker enzymes, TNF-α and IL-6 and serum nitric oxide level in isoproterenol induced acute myocardial ischemia rats. This indicated their potential to be used as cardiovascular drugs.

Catalpol

The roots of Rehmannia glutinosa contain iridoid glucoside called catalpol. Iridoids are monoterpenes which are sud divided into four classes namely iridoid glycosides, non-glycosidic iridoids, secoiridoids and bisiridoids. The cyclopenta-[c]pyran system is the distinctive feature of iridoïd glycoside. Catalpol could improve the endocrine function of the hypothalamic-pituitary-adrenocortical axis and alleviate the structural damage of hypothalamus in Alzheimer's disease. It also provided protection against cerebral ischaemia/reperfusion injury and lipopolysaccharide-induced acute lung injury. Studies showed hypoglycemic effect of catalpol in streptozotocin-induced diabetic rats. Analgesic and chemotherapeutic effect of catalpol were also reported. By the activation of Notch1 signaling pathway catalpol renders a protective effect on cardiotoxic rats.

Calycosin and gallic acid

Calycosin and Gallic acid are obtained from the herb Radix Astragali and Radix Paeoniae respectively. Radix Astragali, of the family fabaceae contains various isoflavones and isoflavonoids like calycosin-7-b-D-glucoside, ononin, calycosin and formononetin. Calycosin suppressed breast cancer cell growth via regulation of insulin like growth factor 1 receptor pathways. It also possesses neuroprotective and anti-hyperglycemic activities. Calycosin has a protective effect in endothelial cells against hypoxia-induced barrier impairment. In isoproterenol induced myocardial necrosis of rats, calycosin and gallic acid synergistically inhibited the infiltration of neutrophils and maintained membrane integrity.

Carnosic acid

Carnosic acid is the major diterpene of rosemary plant Rosmarinus officinalis. Rosemary has several
Table 1: Phytoconstituents protective against isoproterenol induced myocardial necrosis

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Class</th>
<th>Dose</th>
<th>Effect of phytoconstituents on various parameters</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alliin</td>
<td>Organo sulphur</td>
<td>80 mg/kg oral</td>
<td>Decrease in CK-MB, LDH, AST, ALT, HMG CoA reductase.</td>
<td>Lipid-lowering effect.</td>
<td>Sangeetha and Darlin. 2007</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Organo sulphur</td>
<td>10 mg/kg oral</td>
<td>Decrease in CK-MB, LDH, and TNF-α, IL-1β.</td>
<td>Regulated pro-inflammatory factors expressions.</td>
<td>Liu et al. 2009.</td>
</tr>
<tr>
<td>Coptisine</td>
<td>Alkaloid</td>
<td>100 mg/kg oral</td>
<td>Decrease in CK-MB, LDH, AST, ALT. Increase in SOD, CAT, GPT, GPX, GSSH.</td>
<td>Strong antioxidant activity, inhibited RhoA/ROCK expression.</td>
<td>Gong et al. 2012</td>
</tr>
<tr>
<td>Crocin</td>
<td>carotenoid</td>
<td>20 mg/kg oral</td>
<td>Decrease in Left ventricular end diastolic pressure. Increase in SOD, CAT.</td>
<td>Maintained redox status of cell, antioxidant, anti-hipoedamic.</td>
<td>Goyal et al. 2010</td>
</tr>
<tr>
<td>Cinnamic acid &amp; Cinnamaldehyde</td>
<td>Phenolic acid</td>
<td>150 mg/kg oral</td>
<td>Decrease in creatine kinase, lactate dehydrogenase, TNF-α, interleukin, malondialdehyde. Increase in Serum nitric oxide (NO) level.</td>
<td>Anti-oxidative, Anti-inflammatory properties and by increasing Nitric oxide level.</td>
<td>Fansong et al. 2013</td>
</tr>
<tr>
<td>Catalpol</td>
<td>Iridoid glucoside</td>
<td>40 mg/kg oral</td>
<td>Decrease in LDH, CK-MB .Increase in SOD.</td>
<td>Activation of Notch1 signaling pathway.</td>
<td>Jing Zeng et al. 2013</td>
</tr>
<tr>
<td>Calycosin and Gallic acid</td>
<td>Flavonoid, Phenolic acid</td>
<td>40 mg/kg, i.p &amp; 8 mg/kg, i.p</td>
<td>Decrease in myeloperoxidase (MPO) &amp; malondialdehyde (MDA) Increase in SOD, CAT, GPT, GPX, GSSH.</td>
<td>Suppressed neutrophil infiltration and prevented myocardial damage.</td>
<td>Cheng et al. 2015</td>
</tr>
<tr>
<td>Carnosic acid</td>
<td>Polyphenolic diterpene</td>
<td>100 mg/kg oral</td>
<td>Decrease in Troponin I, CK-MB, LDH, SGOT &amp; SGPT. Increase in vitamin C &amp; SOD, CAT, GSH, GST, and GPX.</td>
<td>Enhanced the nuclear translocation of Nrf2 and upregulated the phase II/antioxidant enzyme activities.</td>
<td>Bidya et al. 2014</td>
</tr>
<tr>
<td>Diosgenin</td>
<td>Sapogenin</td>
<td>80 mg/kg oral</td>
<td>Decrease in CK-MB &amp; β-glucuronidase, β-N-acetyl glucosaminidase, β-D- galactosidase, Ca²⁺-ATPase, Mg²⁺-ATPase activity. Increase in Na⁺/K⁺ ATPase.</td>
<td>Antioxidant and membrane stabilizing potential.</td>
<td>Salimeh et al. 2011</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>Flavonoid</td>
<td>20 mg/kg oral</td>
<td>Decrease in creatine kinase-MB, troponin-T and lactate dehydrogenase 1 and 2- isoenzymes. Increase in superoxide dismutase, catalase, glutathione peroxidase.</td>
<td>Free radical scavenging and antioxidant effects.</td>
<td>Prince. 2013</td>
</tr>
<tr>
<td>Epigallocatechin gallate</td>
<td>Flavonoid</td>
<td>30 mg/kg oral</td>
<td>Decrease in Thiobarbituric acid reactive substances, lipid hydroperoxides.</td>
<td>Free radical scavenging and antioxidant effects.</td>
<td>Devika and Prince 2008.</td>
</tr>
<tr>
<td>Compound</td>
<td>Dose</td>
<td>Mode</td>
<td>Effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferulic acid and Ascorbic acid</td>
<td>20mg/kg oral, 80mg/kg oral</td>
<td>decrease in lipid peroxidation and LDH, CPK, SGOT, and SGPT.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycyrrhizic acid triterpene saponin glycoside</td>
<td>20 mg/kg, i.p</td>
<td>decrease in 8-isoprostane, necrosis, hypertrophy, and nuclear pyknosis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolaviron flavonoid</td>
<td>200 mg/kg, oral</td>
<td>decrease in Creatine phosphokinase, lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase &amp; aspartate aminotransferase, malondialdehyde, total cholesterol, triglycerides and low-density lipoprotein. Increase in superoxide dismutase, catalase, total glutathione, catalase, reduced glutathione.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lycopene carotenoid</td>
<td>10 mg/kg, oral</td>
<td>decrease in ST segment, hemodynamic changes (i.e. systolic, diastolic and mean arterial pressure), myeloperoxidase and Caspase-3 protease activity.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Mangostin xanthone</td>
<td>200mg/kg oral</td>
<td>decrease in b-D-glucuronidase, b-D-galactosidase, b-D-N-acetyl glucosaminidase, acid phosphatase and cathepsin-D, TNF-α and COX-2.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matrine alkaloid</td>
<td>200 mg/kg oral</td>
<td>decrease in lactic dehydrogenase, glutamic oxaloacetic transaminase and creatine kinase, improved the left ventricular (LV) dysfunction, including increased lipid peroxidation product malondialdehyde in plasma. Increase in superoxide dismutase, catalase and glutathione peroxidase.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morin flavonoid</td>
<td>20 mg/kg, oral</td>
<td>decrease in creatine phosphokinase, lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marmesin furanocumarin glycoside</td>
<td>200 mg/kg oral</td>
<td>decrease in serum enzyme levels, ST elevation lipid peroxidation and β-glucuronidase. Increase in R amplitude. Membrane stabilizing action by inhibiting the release of β-glucuronidase from the membrane.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Type</td>
<td>Dosage</td>
<td>Effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neferine</td>
<td>Alkaloids</td>
<td>10 mg/kg, oral</td>
<td>Decrease in Serum marker enzymes and lipid peroxidation products. Increase in high density lipoprotein cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinapic acid</td>
<td>Phenolic acid</td>
<td>12 mg/kg, oral</td>
<td>Decrease in cardiac hypertrophy, heart cholesterol, triglycerides, free fatty acids serum low density and very low density lipoprotein cholesterol, ST-segments. Increase in high density lipoprotein cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tannic acid</td>
<td>Phenolic acid</td>
<td>40 mg/kg, ip</td>
<td>Decrease in marker enzymes and tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), Increase in endogenous anti oxidants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanillic acid</td>
<td>Phenolic acid</td>
<td>10 mg/kg, oral</td>
<td>Decrease in Serum cardiac troponins, and lipid peroxidation products, interleukin-1β, interleukin-6 and tumor necrosis factor-α, ST segments. Increase in endogenous antioxidants,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>Alkaloids</td>
<td>25μg/kg, i.p</td>
<td>Decrease in creatine kinase-MB, serum glutamate pyruvate transaminase and lactate dehydrogenase and troponin-T in the serum, thiobarbituric acid reactive substances and lipid hydroperoxides. Increase in Superoxide dismutase, catalasase, glutathione peroxidase and reduced glutathione, Na (+)/K (+)-ATPase.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincosamide</td>
<td>Alkaloids</td>
<td>40 mg/kg oral</td>
<td>Decrease in troponin-T, creatine kinase-MB, lactate dehydrogenase, glutamate pyruvate transaminase, as well as cardiac lipid peroxidation Increase in Cellular antioxidants.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zingerone</td>
<td>Vanillyl acetone</td>
<td>6 mg/kg, oral</td>
<td>Decrease in Lactate dehydrogenase isoenzymes 1 and 2 bands, plasma lipid peroxidation products. Increase in Nonenzymatic antioxidant.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diterpenoid constituents like rosmarinic acid, carnosol, and carnosic acid. Over 80% of the antioxidant properties of rosemary extract are predictably due to carnosic acid and carnosol. Carnosic acid was considered to be beneficial in the prevention of chronic neurodegenerative diseases. Kar et al. illustrated the anti-proliferative and anti cancer properties of carnosic acid. It is also endowed with antimicrobial, anti-inflammatory and anti nephrotoxicity properties. Nuclear translocation of Nrf2 (nuclear factor erythroid 2–related factor 2) and phase II/antioxidant enzyme activities were increased in rats which are pretreated with carnosic acid during isoproterenol induced myocardial necrosis.

**Diosgenin**

Dioscin which is found in yam (Dioscoreaspp.) is a steroidal saponin with diosgenin as its aglycone. 2.7% of dioscin and 0.004% of diosgenin is present in cultivated yam, and 0.12-0.48% is present in wild yam. Diosgenin is a phytosterogen that can be chemically changed into a hormone called progesterone. It was used to make the first birth control pills in the 1960. Diosgenin is a very useful compound to control hyperlipidemia. It enhanced bone development by increasing the production and secretion of Type 1 collagen. It exhibited anticarcinogenic activity and antiviral activity against hepatitis C virus by significantly reducing the levels of viral ribonucleic acid and viral proteins. By its antioxidant property diosgenin reversed the membrane-bound enzyme activity and in doing so it maintained the normal electrolyte concentration suggesting the protective action of diosgenin in isoproterenol induced myocardial infarction.

**Epicatechin**

(-) Epicatechin is a flavonoid isolated from the bark of *Pterocarpus marsupium*. Unfermented cocoa beans contain 120–180 g/kg of polyphenols with (-)-epicatechin being the main polyphenolic compound approximating...
Table 2: Structure and iupac name of phytoconstituents

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Structure</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alliin</td>
<td><img src="image" alt="Alliin structure" /></td>
<td>2 amino-3[(S)-prop-2-enylsulfanyl] propanoic acid.</td>
</tr>
<tr>
<td>N-acetyl cysteine</td>
<td><img src="image" alt="N-acetyl cysteine structure" /></td>
<td>(2R)-2-acetamido-3-sulfanylpropanoic acid.</td>
</tr>
<tr>
<td>Coptisine</td>
<td><img src="image" alt="Coptisine structure" /></td>
<td>6,7-Dihydro-bis(1,3)benzodioxolo(5,6-a:4',5'-g)quinolizinium.</td>
</tr>
<tr>
<td>Crocin</td>
<td><img src="image" alt="Crocin structure" /></td>
<td>bis[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]oxan-2-yl</td>
</tr>
<tr>
<td>Cinnamic aldehyde</td>
<td><img src="image" alt="Cinnamic aldehyde structure" /></td>
<td>3-Phenyl-2-propenal.</td>
</tr>
<tr>
<td>Cinnamic acid</td>
<td><img src="image" alt="Cinnamic acid structure" /></td>
<td>3-Phenyl-2-propenoic acid.</td>
</tr>
<tr>
<td>Catalpol</td>
<td><img src="image" alt="Catalpol structure" /></td>
<td>(1aS,1bS,2S,5aR,6S,6aS)-6-Hydroxy-1a-(hydroxymethyl)-1a,1b,2,5a,6,6a-hexahydrooxirenol[4,5]cyclopyran-2-yl β-D-glucopyranoside.</td>
</tr>
<tr>
<td>Calycosin</td>
<td><img src="image" alt="Calycosin structure" /></td>
<td>7, 3′-dihydroxy-4′-methoxyisoflavone.</td>
</tr>
</tbody>
</table>
Gallic acid
3, 4, 5-Trihydroxybenzoic acid.

Carnosic acid
(4αR,10αS)-5, 6-dihydroxy-1, 1-dimethyl-7-propan-2-yl-2, 3, 4, 9,10,10a-hexahydrophenanthrene-4a-carboxylic acid.

Diosgenin
(3β,25R)-Spirost-5-en-3-ol.

Epicatechin
(2R,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol.

Epigallocatechin Gallate
(2R,3R)-2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl 3,4,5-trihydroxybenzoate.

Ferulic acid
4-Hydroxy-3-methoxycinnamic acid.

Glycyrrhizic acid
(3b,20b)-20-Carboxy-11-oxo-30-norolean-12-en-3-yl2-O-b-D-glucopyranuronosyl-a-D-glucopyranoside uronic acid.
Kolaviron

GB-1 \((R_1-H, R_2-H)\), GB-2 \((R_1-OH, R_2-H)\)
Kolaflavanone [garcinianin] \(R_1-\text{OH} R_2-\text{Me}\)

Lycopene

\(\text{1,6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-1,6,10,14,19,23,27,31-\text{Octamethyl-2,8,10,12,14,16,18,20,22,24,26,30-dotriacontatriacontane}\)

\(\text{α-Mangostin}\)

\(\text{1,3,6-Trihydroxy-7-methoxy-2-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one}\)

Matrine

\(\text{1H,5H,10H-Dipyrido}[2,1-f:3',2',1']ij][1,6]naphthyridin-10-one\)

Morin

\(\text{3,5,7,2',4'-pentahydroxyflavone}\)

Marmesinin

\(\text{2-[(2S)-7-Oxo-2,3-dihydro-7H-furo[3,2-g]chromen-2-yl]-2-propanyl β-D-glucopyranoside}\)

Neferine

\(\text{4-[(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinyl)methyl]-2-[(6-methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydro-7-isoquinolinyl)oxy] phenol}\)

Sinapic acid

\(\text{2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid}\)
35%. Structurally, (−)-epicatechin is composed of two phenyl rings linked by a chromene ring with a 4-hydroxyl group. It decreased the liability of low density lipoprotein to oxidation which prevents the initiation of artherosclerosis\(^{52}\). Epicatechins are neuroprotective and anti allergic. They inhibited prostate cancer cell proliferation, potentially by suppressing androgen receptor activation and androgen receptor-regulated gene transcription\(^ {53}\). Pretreatment with epicatechin prior to exposure of gamma (\(\gamma\)) radiation prevented hepatic and testicular damage. Given its antioxidant capacity, (−)-epicatechin has been studied as a cardioprotective therapy. Cardioprotection owing to free radical scavenging and antioxidant effects, was observed when rats were pretreated with (−)-epicatechin following stimulation of myocardial infarction via isoproterenol injection\(^{54}\).

Epigallocatechin gallate (EGCG)

Epigallocatechin gallate is present in the leaves of Camellia sinensis commonly called as green tea leaves. (−)-Epigallocatechin gallate (EGCG), (−)-
epigallocatechin, (−)-epicatechin gallate, and (−)-epicatechin are some of the catechins present in this plant. Epigallocatechin gallate (EGCG) constitutes a major portion among all catechins available in green tea. The presence of a trihydroxy B-ring and a gallate group are accountable for antioxidant activity of EGCG. Epidemiological and animal studies indicate that EGCG showed protective activity in neurological disorders and in cancer. EGCG is a potent inhibitor of many enzymes that are involved in the fatty acid biosynthesis of Plasmodium falciparum, thus giving it an antimalarial effect. Due to its free radical scavenging and antioxidant effects, EGCG manages the tissue defense system extending cardioprotection to rats which suffer isoproterenol induced myocardial infarction.

Ferulic acid

Ferulic acid is one among the many ample phenolic acids in plants and also present in high concentrations in foods like navy bean, corn bran, wheat bran, eggplant, artichokes and beets. It can be found free, dimerized or esterified with proteins and polysaccharides in the cell wall. Ferulic acid contains an yellow liquid of cis isomer and a white crystal of trans isomer, the latter corresponding to 90% of its natural occurrence. Ferulic acid is a useful molecule for antiviral therapy. It is a hepatitis protective agent against toxins commonly ingested in the diet. It also possesses chemopreventive activity against colon cancer. Due to its ability to stop radical chain reactions by resonance and polymerization, ferulic acid offers protection against UV-radiation. Ascorbic acid, is a naturally occurring water soluble vitamin which has high antioxidant property. Studies confirmed the protective role of a mixture of antioxidants containing vitamin C, ferulic acid, and phloretin on human skin from the harmful effects of radioactive rays. When ferulic acid was given along with ascorbic acid, they synergistically protected the myocardium from oxidative stress by virtue of their lipid peroxidation and antioxidant activities in rats.

Glycyrrhizic acid

Glycyrrhizic acid is a triterpene saponin glycoside obtained from the roots of the plant Glycyrrhiza Glabra (Liquorice), Leguminosae family. It is a conjugate of two molecules, namely glucuronic acid and glycyrrhetic acid. Liquorice contains more than 20 triterpenoids and nearly 300 flavonoids. Among them, glycyrrhizin (GL), 18β-glycyrrhetic acid (GA), liciritigenin, licochalcone A, and glabridin are the main active components. Glycyrrhizin is many times sweeter than sugar. Reports demonstrate glycyrrhizic acid attenuated oxidative damage caused by chemically induced liver damage in rats. In many countries, viral hepatitis and dermatitis are treated by using glycyrrhizic acid. It is also known to have activities against inflammation, ulcer, diabetes and antiviral activities. As it has high antioxidant activity and could reduce cardiac lipid hydroperoxide and 8-isoprostane level, glycyrrhizic acid treatment was found to be efficient against isoproterenol induced acute myocardial infarction in rats.

Kolaviron

Kolaviron is a biflavonoid compound obtained from the seeds of Garcinia kola (family: Guttiferae) which is commonly known as bitter kola. Kolaviron is the predominant component in G. kola and it is a mixture of biflanones (GB1, GB2 and kolaflavonone). Many studies have established the anti-inflammatory, gastrointestinal and hepatotoxic activity of kolaviron in animal models and in cell culture. Kolaviron has been reported to reduce the level of glucose and cholesterol in diabetic animals. By opening potassium channels and preventing release of intracellular calcium kolaviron exerts vaso relaxant effects in smooth muscle. Since kolaviron was reported to elicit strong antioxidant activity, the cardioprotective effects of kolaviron in rats intoxicated with isoproterenol (ISO) was studied. Supplementation with kolaviron caused significant elevation of cardiac antioxidant enzymes, and reduced MDA levels.

Lycopene

Lycopene is the major carotenoid present in tomatoes. Lycopene is a C40-carotenoid made up of eight isoprene units; making it a tetraterpene. Lycopene cyclase catalyzes the conversion of lycopene to β-carotene by substitution of two β-rings at each end of the straight chain carotene. This deep red color pigment has eleven conjugated double bonds which are accountable for its antioxidant activity. Lycopene shows an array of biological effects. It acts as a moderate hypcholesteremiac agent, changes neurochemical defects, oxidative imbalance, apoptosis and provides useful approach in the treatment of neurodegenerative disease. Anti carcinogenic activities in liver, lungs, mammary gland and skin of animal models were also reported. Findings exposed the cardioprotective property of lycophene against isoproterenol induced oxidative stress and cardiotoxicity in rats. These experimental activities are mediated by means of antioxidant potency and free radical scavenging activity of lycophene.

α-Mangostin

α-Mangostin is obtained from Garcinia mangostana (family: Guttiferae). Many xanthones have been extracted from leaves, whole fruit and heartwood. The first among them is α-mangostin and was isolated in 1855. Other xanthones like xanthogentin, garatin, 8-deoxygartanin, garcineone A, B, C, D and E are also obtained from mangosteen-fruit. The reno protective effect of α-Mangostin was evaluated by perez-rojas et al. It attenuated the neurotoxicity induced by amyloid beta Aβ(1-40) oligomers, suggesting the great potential of it to be a candidate for Alzheimer disease treatment. The antibacterial, antifungal, antiplasmodial and anti inflammatory activities were its early reports. The impact of α-Mangostin on lipid peroxidation during myocardial infarction in rats induced by isoproterenol was evaluated by devi and vijayaraghavan. α-Mangostin conserved the myocardial membrane integrity and controlled deviating TNF-α and COX-2 (cyclooxygenase-2) factors by mitigating isoproterenol involved oxidative stress and cellular damage efficiently.

Matrine

Matrine
Matrine is an alkaloid purified from dried roots of *Sophora flavescens* Aiton (Leguminosae). The roots include two major tetracyclo-quinolizidine alkaloids (matrine and oxymatrine) as its primary components. Matrine has a wide band of pharmacological actions including antimicrobial, antiviral, antiinflammatory, antidiabetic, antiobesity, neuroprotective and hepatoprotective activities. Matrine was used for treatment of bacillary dysentery, enteritis and malignant pleural effusion. Matrine prevented the proliferation of various types of cancer cells chiefly through intervention of cell cycle arrest. The protective role of matrine on cardioprotection against isoproterenol induced cardiotoxicity was exhibited through its antioxidant property.

Mohin

Mohin hydrate (morin) is a natural yellow crystalline polyphenolic compound coming from branches of *Morus alba* L (white mulberry) family: Moraceae. Providing mohin hydrate to immune cells had a positive immunoprotective effect that showed its possible use in inflammation related diseases. Studies suggested morin as a capable anti-virulence therapeutic agent for healing *Staphylococcus aureus* infections. A successful attempt was made to study the effect of morin hydrate in gentamicin induced nephrotoxicity. In addition, morin also exerted various activities like, suppression of xanthine oxidase, deterrence of oxidation of low-density lipoprotein, immunomodulation, antitumor activity, antioxidant and hypouricemic activities. Morin rendered cardioprotective benefits in isoproterenol induced myocardial infarcted rats by regulating lipid metabolism.

Marmesinin

Marmesinin is a linear furanocoumarin, found in spineous tree *Aegle marmellos* which is commonly known as bael: family Rutaceae. Active principles found in the leaves of *Aegle marmelose* are rutin, b-sitosterol-b-glucoside and marmesinin. Administration of furano coumarin prevented deoxyribonucleic acid from forming adducts in various tissues of rats. It also increased the antioxidant enzyme levels in liver and lung evidencing its radical scavenging properties. Pretreatment with marmesinin inhibited the delivery of β-glucuronidase from the cellular fractions in isoproterenol administrated rats. This is done by virtue of its stabilizing effect on membranes.

Neoferine

Neoferine is a bisbenzyl isoquinoline alkaloid extracted from the seeds of *Nelumbo nucifera* Gaertn (lotus). The major phytochemicals present in lotus seeds are roemerine, nelumbine, dauricine, liensine, isoliensinine, lotusine, nuciferine, and neoferine. Of these, neoferine is the major isoquinoline alkaloid obtained, along with liensine and isoliensinine. Anticancer potential and anti-arrhythmic action of neoferine were reported earlier. It also subdued the increase of vascular smooth muscle cells and significantly prevented bleomycin-induced pulmonary fibrosis. Investigation of neoferine against isoproterenol induced myocardial infarction showed that it is a strong antioxidant and can be used as a potent cardioprotective agent against oxidative stress.

Sinapic acid

Sinapic acid is a hydroxy cinnamic acid. Hydroxycinnamic acids possess a phenylpropanoid C6-C3 structure and are the main subgroup of phenolic acids with ubiquitous distribution in the plant kingdom. Sinapic acid exists in both free and ester form. Citrus fruits hold diverse amounts of sinapic acid, of which lemon (*Citrus limon*) has maximum amount of 72.11μg/g and mircocottange (*C. reticulate, C. sinensis*) has 50.1μg/g. Sinapic acid has a potential and dose-dependent anti mutagenicity character. It selectively kills the pathogenic bacteria leaving beneficial lactic acid bacteria alive. Anti hyperglycemic activity and neuroprotective effects of sinapic acid were reported. Sinapic acid has the potential to be used as a curative approach for inhibiting hepatic inflammation. Its free radical scavenging ability, membrane stabilizing features and antilipidaemic potential could be the possible mode for its action against myocardial infarction in rats caused by isoproterenol.
isolated from the leaves of the plant by techniques such as tissue culture, cell culture, and shoot culture. Vincristine exhibits potent pharmacological activities. It showed antiparasitic effects against Trypanosoma cruzi 107. On oxidation vinblastine is converted to vincristine which arrests mitosis in metaphase. Vincristine is effective for treating wilkins’s tumour, acute lymphoblastic leukaemia, hodgkin’s disease and neuroblastoma 108. Apart from this, the cardio protective activity of vincristine in isoproterenol mediated cardiac necrosis in rats has been evaluated and it mediated the protective outcome by its free radical scavenging property 109.

Vincosamide

The leaves extract of Moringa oleifera Lam. generally known as drumstick leaves (Family- Moringaceae) contains an indole alkaloid called N, α-L-rhamnopyranosyl vincosamide 110. M. oleifera contains diverse phytochemicals counting saponins, alkaloids, terpenoids, flavonoids and phenolic acids. The leaves were reported to show protection from radio-active rays and were effective in thyroid and cancer treatments. Pretreatment of rats with vincosamide considerably reduced the high level of cardiac marker enzymes near to regular levels evidently presenting the free radical scavenging property and cardioprotective activity of this alkaloid 110.

Zingerone

Zingerone is the least pungent component present in Zingiber officinale, (family: Zingiberaceae). Zingerone is primarily present in dry ginger 9.25% 111. Exposure to air or heating converts gingerol into zingerone by retro aldol process 112. Zingerone is known to have potent pharmacological activities. Anti diarrheal, anti inflammatory and anti cancer effects of zingerone were studied extensively 113. A possible mechanism responsible for zingerone’s radio protective effect against X-rays, gamma rays and infrared rays, was that it neutralized radiation-induced reactive oxygen species and oxidative stress by its strong antioxidant potential. Studies showed that zingerone also has potent lipolytic activity 114. Moreover Zingerone behaves as an appetite stimulant, anxiolytic and antimicrobial agent. Recent studies indicated that zingerone also safeguards the myocardium against isoproterenol caused myocardial necrosis in rats by virtue of its antioxidant effect 115.

ABBREVIATIONS

EGC- Electrocardiography, GSH-Reduced Glutathione, HDL-High density lipoprotein, MDA- Malondialdehyde, TBARS- Thiobarbituric acid reactive substances, NFκB- Nuclear factor kappa B, IL-6- Interleukin 6, TNF-α- Tumor necrosis factor alpha.

REFERENCES


46. Ji YB. Active ingredients of traditional chinese medicine: Pharmacology and application 2011; People’s medical publishing house Cp.LTD.

47. Jing Zeng, Feng Huang, Yuanqing Tu, Saichun Wu, Manping Li, Xiaoyun Tong. Protective effect of catalpol on myocardium in rats with isoprenaline-induced myocardial infarcts via angiogenesis through endothelial progenitor cells and notch1 signaling pathway. Pharmaco Pharm 2013; 4:619-627.


