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Protective effects of some medicinal plants against myocardial hypoxia

Abstract: Myocardial hypoxia is one of the main complications of myocardial ischemic injury which have high morbidity and mortality. The aim of this review is to investigate the protective effects of medicinal plants in myocardial hypoxia. The words cardiomyocytes alongside with hypox* or myocardial hypoxia, in combination with some herbal terms such as medicinal plant, phyto* and herb*, were used to search for relevant publications indexed in the Institute for Scientific Information (ISI) and PubMed. Finally after all revisions, 74 articles were included in this study. Available evidence shows that certain medicinal plants and herbal derivatives can exert their myocardial protective effects against hypoxia using several pathways. These mechanisms include antioxidant properties such as savaging reactive oxygen species (ROS) and activation antioxidant pathways, suppressing pro-apoptotic genes and regulate apoptosis pathways, regulating autophagy and related pathways, reducing inflammation and suppress proinflammatory cytokines and pathways, inhibiting intracellular Ca^{2+} influx, antiplatelet aggregation, stimulating the adenosine triphosphate (ATP) generation in mitochondria and mitochondrial respiration, promoting autophagy, regulating hypoxia-inducible factor 1-alpha (HIF-1α) expression, decreasing the expression of angiotensin, reducing cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) and up-regulation of epoxyeicosatrienoic acids (EETs). Thus, clinicians can use the medicinal herbs as an effective treatment against myocardial hypoxia. Post-ischemia and chronic treatment of cardioprotection maybe consider as a therapeutic strategies than short term and pre-treatment methods in clinical setting. Nevertheless, more clinical trial studies are required in order to obtain more reliable results.
Key words: antihypoxic, medicinal plants, reactive oxygen species, myocardial ischemic injury.

Introduction

Myocardial ischemic injury occurs due to severe dysfunction of coronary blood supply and is a leading cause of morbidity and mortality worldwide [1]. This disorder is closely associated with cardiac dysfunction, in particular some aspects of it, such as myocardial stunning, left ventricular remolding, inflammation, fibrosis, neurohormonal activation, cardiomyocyte necrosis, reperfusion injury, haemorhage and microvascular obstraction are causes heart failure [2]. Myocardial ischemic injury is a pathological process that includes augmented cell death, namely, oncosis, apoptosis and infarction [3]. Cardiomyocytes consume large quantities of energy and are very sensitive to lack of energy. During heart attack and eventually hypoxia, cardiac myocytes switch their metabolism to anaerobic respiration, which causes ATP depletion, lactate accumulation, Na^+ and Ca^{2+} overload and due to myocardial contractile dysfunction. Reperfusion results in generation of reactive oxygen species (ROS), what contributes to apoptosis and inflammation and finally myocardial infarction and ischemic reperfusion injury [4].

Currently there are several therapeutic strategies used for treatment, not as effective as could be [4]. As a result, new investigations are considered necessary in this area. Medicinal plants are the cheapest and conventional approach to confronting numerous diseases especially for treatment of heart failure [5-13]. Given that the magnitude of heart disease in human mortality and necessity for new therapeutic strategies to treatment of chronic heart failure are high, this review was prepared to find out the protective effects of medicinal plants in myocardial hypoxic condition and its related complications.

Search for strategies and study design

Key words of interest, such as cardiomyocytes alongside with hypox* or myocardial hypoxia, in combination with some herbal terms, namely medicinal plant, phyto*, and herb* were used to search for relevant publications indexed in the Institute for Scientific Information (ISI) and PubMed. Finally, 74 articles were found with Endnote software (Table 1).

Table 1 – Number of studies present in subsequent databases

Hypox* + Cardiomyocyte + Medicinal plant	PubMed	3
	ISI	1
Hypox* + Cardiomyocyte + Phyto*	PubMed	3
	ISI	1
Hypox* + Cardiomyocyte + Herb*	PubMed	22
	ISI	19
Myocardial hypoxia + Medicinal plant	PubMed	15
	ISI	6
Myocardial hypoxia + Phyto*	PubMed	9
	ISI	9
Myocardial hypoxia+ Herb*	PubMed	68
	ISI	46
Total	PubMed	120
	ISI	82

A standard form, which included items as purpose or the title of the study, intervention, outcome, variables, journal name, intervention period, and article number, was designed. Selection process is presented on Figure 1.

First, full text articles relevant to the purpose of the study were recorded in the form and entered into the study with agreement of researchers. Then, the plants and their products that were reported to be effective to treat myocardial hypoxia and related complications were selected for the study. Articles, where full texts were not accessible, non-English language articles, studies with non-positive effects, review articles, and studies that were not relevant to the principle aim of the current study were excluded after all authors' agreement was achieved. Finally, 74 articles were included into the study.

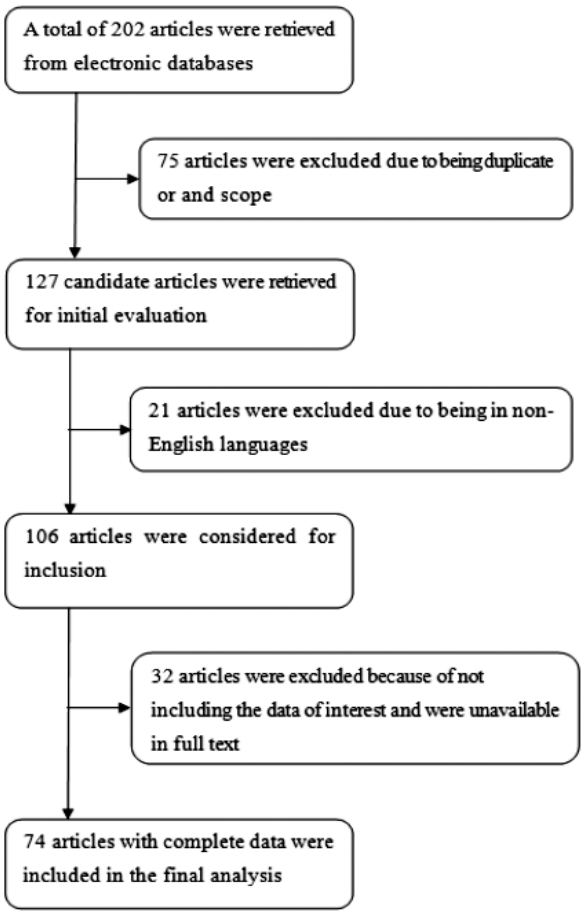

Figure 1 – The process of selection of articles for final analysis.

Results and discussion

Medicinal plants and their compounds can be effective against myocardial hypoxia via various mechanisms of action. Summary of analysis for some of them is provided in Table 2.

Table 2 – Medicinal plants, formula and compounds with cardioprotective effects and mechanisms of action against myocardial hypoxia

Medicinal plants				
References	**Main effects or mechanisms**	**Type of administration**	**Study design**	**Scientific name of the plant**
[14]	Diminishing levels of oxidants generated during hypoxia and within exposure to the mitochondrial site III inhibitor antimycin A and decreasing cell death	Aqueous extract	Experimental (*in vitro*)	*Scutellaria baicalensis* Georgi
[15]	Reducing degenerative intra mitochondrial areas. In addition insert protective effect to reducing number of ATPase particles at the inner mitochondrial membranes and increasing of myocardial capacity for ATP production	Extract	Experimental (*in vitro and in vivo*)	*Ginkgo biloba*
[16]	Increasing the expressions of hypoxia-inducible factor 1alpha (HIF-1alpha), hypoxia-inducible factor 1beta (HIF-1beta) and vascular endothelial growth factor (VEGF) mRNAs and the expressions of HIF-1alpha and VEGF proteins	Solution	Experimental (*in vitro and in vivo*)	Radix et rhizoma *Rhodiolae kirilowii*
[17]	Decreasing $[Ca(^{2+})]i$ contents in cardiac muscel cells and inhibiting the changes induced by Potassium chloride (KCl) in single cardiac myocytes	Powder extract	Experimental (*in vitro*)	*Rhododendron dauricum L.*
[18]	Decreasing the level of MDA, intracellular ROS, release of LDH and apoptosis. Besides enhancement the activity of SOD	Aqueous and ethanolic extract	Experimental (*in vitro*)	*Pseudostellaria heterophylla*
[19]	Increasing mitochondrial ATP-generation capacity (ATP-GC) and ADP-stimulating state 3 respirations and increasing antioxidant capacity. In addition enhancement of cellular glutathione redox cycling and reducing apoptosis	Dried extract	*Ex-vivo*	*Cistanche deserticola*
[20]	Protected myocyte cells against hypoxia via ROS scavenger	Aqueous extract	Experimental (*in vitro*)	*Pogostemon cablin* Blanco
[21]	Reducing apoptosis and oxidative stress via activation of PI3 K/Akt signaling pathway	Aqueous extract	Experimental (*in vitro*)	*Dictamnus dasycarpus* Turcz
[22]	Reducing calcium accumulation, inhibiting caspase-3 activation, and down-regulating protein expression of p-JNK and p-p38MAPK	Extract	Experimental (*in vitro and in vivo*)	*Trichosanthes cucumerina*
Medicinal plants formula				
References	**Main effects or mechanisms**	**Type of administration**	**Study design**	**Herbal compounds/ derivatives**
[23]	Inhibited reduced GSH and also a reduced sensitivity to Ca^{2+}-induced mitochondrial permeability transition. In addition activated both ERK/Nrf2 and PKC epsilon/m ATP-sensitive potassium channel (K-ATP) pathways	Decoction	Experimental (*in vitro*)	Danshen and Gegen composed of *Salviae miltiorrhizae* and *Puerariae lobatae*
[24]	Decreasing calcium accumulation and reducing cell apoptosis by protecting cell membrane skeleton integrity and the mitochondrial function.	Decoction	Experimental (*in vitro*)	Danshen and Gegen

Continuation of table 2

[25]	Up-regulation of epoxyeicosatrienoic acids (EETs)-generating cytochrome P450 enzymes	Extracted Pill	Experimental (*in vitro and in vivo*)	Danshen composed of *Salviae Miltiorrhizae, Notoginseng Radix* and *Borneolum Syntheticum*
[26]	enhancing antioxidant capacity and calcium handling and lead to reducing apoptosis rates	Solution	Experimental (*in vitro*)	Danshen composed of *Salviae Miltiorrhizae, Notoginseng Radix* and *Borneolum Syntheticum*
[27]	Promoting autophagy via activation of the mitogen activated protein kinase/ERK pathway	Solution	Experimental (*in vitro*)	Tongxinluo composed of *Radix ginseng, Hirudo, Eupolyphaga seusteleophaga, Buthus martensi, Scolopendra subspinipes, Periostracum cicadae, Semen ziziphi spinosae, Radix paeoniae rubra, Lignum santali albi, Lignum dalbergiae odoriferae,* and *Borneolum syntheticum*
[28]	Up-regulating proteins which involving in regulation of metabolic process, cell proliferation and stress response.	Solution	Experimental (*in vitro*)	Tongxinluo
[29]	Activating Angptl4-mediated regulation of endothelial barrier integrity through the PPAR-α pathway	Solution	Experimental (*in vitro and in vivo*)	Tongxinluo
[30]	Increasing cell viability and SOD levels and decreased MDA levels. Besides suppressing MDA, cTnT and inflammatory cytokines.	Extract capsule	Experimental (*in vitro and in vivo*)	Yindanxinnaotong composed of *Ginkgo biloba*, *Salvia miltiorrhizae*, *Gynostemma, ynostemmatis*, *Erigerontis herba*, *Allii sativi bulbus*, Radix/rhizoma *notoginseng*, *Crataegi fructus* and *Borneolum*
[31]	Inhibition of mitochondrial permeability transition pore (mPTP) opening via attenuating Ca^{2+} overload and ROS generation	Extract	Experimental (*in vitro*)	Danhong composed of *Salvia miltiorrhiza* Bge and *Carthamus tinctorius* L.
[32]	Reducing in MDA, LDH, cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) and reducing expression of cleaved caspase-3, 8-hydroxydeoxyguanosine (8-OHdG), and increasing SOD activity, Bcl-2/Bax ratio and regulating Akt/Nrf2/HO-1 signaling	Solution	Experimental (*in vitro and in vivo*)	Danhong injection composed of *Salvia miltiorrhiza and Carthamus tinctorius L*+ hydroxysafflor yellow A that are the main active ingredients of Radix *Salvia miltiorrhiza*
[33]	Inhibiting myocardial apoptosis, probably by regulating hypoxia-inducible factor 1-alpha (HIF-1α) expression in cardiomyocytes	Extract Pill	Experimental (*in vitro and in vivo*)	Qishen Yiqi Droping Pill composed of *Salvia miltiorrhiza* Bge, *Pannax notoginseng,* and *Dalbergia odorifera* T. Chen.
[34]	Reducing inflammation of the endothelial cells, inhibiting the activity of LDH, CK and decreasing the level of MDA and increasing SOD activity	Extract	Experimental (*in vivo*)	Yi-Qi-Fu-Mai composed of *Panax ginseng, Ophiopogon japonicas* and *Schisandra* chinensis
[13]	Inhibiting mitochondrial mediated apoptosis and modulating AMP-activated protein kinase (AMPK) activation mediating mitochondrial fission	Powder	Experimental (*in vitro and in vivo*)	Yi-Qi-Fu-Mai
[35]	Reducing $[Ca^{(2+)}]i$ accumulation induced by hypoxia-reoxygenation in ventricular myocytes via supressing I_{NaL} and I_{CaL}	Extract	Experimental (*in vitro*)	Wenxin Keli composed of *Nardostachys chinensis Batal, Codonopsis, Notoginseng, amber,* and *Polygonati*

Continuation of table 2

[36]	Inhibiting autophagy through regulating AMPK-mTOR signaling pathways and increasing cell viability and consequently reduced apoptosis.	Decoction	Experimental (*in vitro*)	XuefuZhuyu decoction composed of *Angelica sinensis (Oliv.) Diels Rehmannia glutinosa Libosch Prunu persica (L.), Batsch, Carthamus tinctorius L., Paeonia Lactiflora Pall. Bupleurum chinense DC, Citrus aurantium L., Glycyrrhiza uralensis Fisch., Platycodon grandiflorum (Jacq.) A.DC. Ligusticum chuanxiong Hort.* and *Achyranthes bidentata Blume*
[37]	Increasing cardiomyocytes survival by regulating stress-responsive mitogen-activated protein kinases (MAPK) pathways and phosphatidylinositol 3-kinase (PI3K)-Akt pathway for cell survival was restored by the herbal compounds	Solution	Experimental (*in vitro*)	Tanshinone IIA from S*alvia miltiorrhiza Bunge* and astragaloside IV from *Astragalus membranaceus*
[38]	Decreasing myocardium infarct size, reducing apoptosis and myocardial myeloperoxidase (MPO). In addition decreasing MDA, calcium accumulation, LDH, creatine kinase MB isoenzyme (CK-MB), and cardiac troponin I (cTn-I) activity	Solution	Experimental (*in vitro and in vivo*)	Sheng-Mai-San composed of ginsenoside Rb1 (ginsenosides of *Panax ginseng*), ruscogenin, (saponins of radix *ophiopogonis*) and schisandrin (lignans of *Fructus schisandrae*)
[39]	Activating of Peroxisome proliferator activated receptor gamma co-activator (PGC-1α) and maintenance of mitochondrial functions via involving the activation of AMPK phosphorylation	Decoction	Experimental (*in vitro and in vivo*)	Yiqihuoxue *Astragalus membranaceus, Angelica sinensis, Panax ginseng, Ligusticum wallichii,* and *Panax notoginseng*
[40]	Regulating of Ca^{2+} influx, reducing oxidative stress and apoptotic proteins (Mainly by *Salvia miltiorrhiza Bunge*)	Aqueous extract	Experimental (*in vitro*)	Xin-Ke-Shu that composed of *Salvia miltiorrhiza Bge, Pueraria lobata, Ohwi, Panax notoginseng F.H. Chen., Crataegus pinnatifida Bunge* and *Aucklandia lappa Decne*
[41]	Promoting mitochondrial function through increasing respiration, ATP-coupled respiration, and spare capacity of mitochondria in response to hypoxia	Solution	Experimental (*in vitro and in vivo*)	Shenmai formula composed of *Panax ginseng* and *Ophiopogonis*
[42]	Activating RISK pathway and reducing apoptosis. In addition insert cardioprotective effects by antioxidant activity	Decoction	Experimental (*in vitro*)	Gualou Xiebai composed of *Trichosanthis Fructus* and *Allii Macrostemonis Bulbus*
Medicinal plants compounds				
References	**Main effects or mechanisms**	**Type of administration**	**Study Design**	**Herbal compounds/ derivatives**
[43]	Improving hypoxic contractile recovery. Main mechanism associated with restoration of tissue ionic concentrations and reducing the release of ATP metabolites and creatine kinase from the hypoxic hearts	Solution	Experimental (*in vivo*)	Tanshinone VI derived from S*alvia miltiorrhiza Bunge*
[44]	Reducing infarct size and preventing the increase in superoxide dismutase-mRNA and inhibition of $45Ca^{2+}$ influx	Solution	Experimental (*in vivo*)	Trilinolein derived from *Panax pseudoginseng*
[45]	Increasing in Cu.Zn-superoxide dismutase (SOD) activity and indicating antioxidant effect that insert its myocardial protective effect	Solution	Experimental (*in vivo*)	Trilinolein derived from *Panax pseudoginseng*

Continuation of table 2

[46]	Augmenting the force recovery from reperfusion and arrhythmia via decreasing [Cl-] i in non-hypoxic myocytes and modulation of intracellular Cl- homeostasis	Extract	Experimental (*in vitro and in vivo*)	Sasanquasaponin derived from *Camellia oleifera*
[47]	Decreasing lactate dehydrogenase (LDH) release, malondialdehyde, oxidized glutathione (GSSG) contents and reactive oxygen species (ROS) levels. In addition increasing activities of Glutathione (GSH) contents and superoxide dismutase, catalase and glutathione peroxidase. Besides reducing calcium accumulation in cardiomyocytes.	Extract	Experimental (*in vitro*)	Sasanquasaponin derived from *Camellia oleifera*
[48]	Reducing in oxidized glutathione and lipid peroxidation	Extract	Experimental (*in vivo*)	Oleuropein derived from *Olea europaea* oil
[49]	Protecting rat aorta endothelial cells against hypoxia and stimulating nitric oxide (NO) release from endothelial cells, cytoprotection, KATP channel opening and venous thrombosis inhibiting	Solution	Experimental (*in vitro*)	Cyclovirobuxine D derived from *Buxus microphylla*
[50]	Up-regulating of GSH and inhabitation of deplete cellular GSH level. The 12-O-tetradecanoylphorbo-13-acetate response element or the antioxidant response element may be involved in the transactivating actions of andrographolide on the catalytic subunit (GCLC) and modifier subunit (GCLM) promoters	Solution	Experimental (*in vitro*)	Andrographolide derived from *Andrographis Paniculata*
[51]	Down-regulating gene expression levels of pro-apoptotic genes such as Bax and Fas proteins. But it up-regulating Bcl-2 and Bcl-xl proteins. In addition inducing the anti-oxidant enzymes SOD and CAT	Extract	Experimental (*in vitro*)	Leonurine derived from *Herba leonuri*
[52]	Insert anti-apoptotic effects by activating the PI3K/AKT/GSK3β pathway and reduced apoptosis	Solution	Experimental (*in vitro and in vivo*)	Leonurine
[53]	Increasing the Akt phosphorylation, reducing gene expression of Bcl-2, but it reducing the gene expression of Bax in vivo. In addition increasing the expression of HIF-1α but also the expression of survivin and VEGF	Extract	Experimental (*in vitro and in vivo*)	Leonurine
[54]	Down-regulating gene expression levels of proapoptotic genes (Bax, Fas and caspase-3) and up-regulating Bcl-2. Besides it can increasing in SOD content	Methanolic extract	Experimental (*in vitro*)	Hirsutine derived from *Uncaria rhynchophylla*
[55]	Modulating the PI3K/Akt pathway and reducing hypoxia-induced apoptosis	Solution	Experimental (*in vitro*)	3,5-dimethoxy-4-(3-(2-carbonyl-ethyldisulfanyl)-propionyl) derived from *Herba Leonuri*
[56]	Reducing cardiac Troponin I (cTnI) secretion in serum and attenuated the Ca2+ overload in cardiomyocytes and modulated the ATP-sensitive potassium channel (KATP) signaling pathway	Solution	Experimental (*in vitro and in vivo*)	Saponins derived from *Panax ginseng*
[57]	Attenuating A/R-induced inflammatory response and apoptosis that related to the TLR4/NF-κB signaling pathway	Solution	Experimental (*in vitro*)	Resveratrol derived from wide variety of plant species

Continuation of table 2

[58]	Up-regulating miR-133 expression via activating MAPK ERK1/2 pathway and enhanced cell resistant to hypoxic condition	Extract	Experimental (*in vitro*)	Tanshinone IIA derived from *Salvia miltiorrhiza*
[59]	Reducing myocardial infarct size, serum levels of TNF-alpha, and platelet aggregation. Besides reducing apoptosis via down-regulated the expression of cleaved caspase-3, and up-regulating the expression of phosphorylated Akt	Solution	Experimental (*in vitro and in vivo*)	Citric acid and L-malic acid derived from *Fructus choerospondiatis*
[60]	Attenuating inflammation of cardiomyocytes via inhibiting ERK1/2 and JNK signaling pathways	Solution	Experimental (*in vitro*)	Sparstolonin B derived from *Sparganium stoloniferum*
[61]	Inhibiting the adhesion between human cardiac microvascular endothelial cells (HCMECs) and polymorphonuclear leukocyte(PMN), through down regulation of the expression and phosphorylationofp38 MAPK	Extract	Experimental (*in vitro*)	Astragalus polysaccharide derived from *Astragulus*
[62]	Attenuating myocardial iscemic via activating hypoxia inducible factor-1a (HIF-1 α)/inducible nitric oxide synthase (iNOS) pathway. Besides up-regulating of the Bcl2 protein and down-regulating of the caspase3 protein	Solution	Experimental (*in vitro*)	Astragaloside IV derived from *Astragalus membranaceus*
[63]	Stimulated the mitochondrial ATP generation and mitochondrial respiration. Up-regulating of cellular glutathione redox cycling and reducing apoptosis	Solution	*Ex-vivo*	β-sitosterol derived from *Cistanche deserticola*
[64]	Protecting hypoxia induced inflammation by attenuating cyclooxygenase-2 (COX-2) mediated cell apoptosis, and the death of endothelial cells through oxidative stress reduction	Decoction	Experimental (*in vitro and in vivo*)	Baicalein sulfates/ glucuronides and wogonin ssulfates/glucuronides derived from *Scutellaria baicalensis* Georgi
[65]	Decreasing LDH release and increasing in Bcl-2 and a decrease in active caspase-3 expression and suppress apoptosis by activating the PI3K/ Akt/eNOS signaling pathway	Solution	Experimental (*in vitro and in vivo*)	Breviscapine derived from *Erigeron breviscapus*
[66]	Decreasing serum levels of CK-MB, TNF-α, IL-6, LDH, SOD, and MDA. Besides, can cause increasing SOD activity and decreased MDA content in myocardial tissue. In addition preventing myocardial injury via regulation of Nox/NF-κB/AP1 pathway	Solution	Experimental (*in vitro and in vivo*)	Salidroside derived from *Rhodiola rosea*
[67]	Reversing Bax/Bcl-2 ratio and inhibiting the activities of caspase-3 and caspase-9, increasing mitochondrial function, by reducing ROS accumulation, improving mitochondrial membrane potential and decreasing intracellular calcium concentration and supressing apoptotic myocyte death by reducing Akt/GSK-3β pathway activating	Solution	Experimental (*in vitro*)	Asiatic acid derived from *Centella asiatica*
[68]	Inhibiting apoptosis by reversing mitochondrial dysfunction, due to activation of GLP-1R and PI3K/AKT signaling pathway and reducing oxidative stress.	Solution	Experimental (*in vitro*)	Geniposide derived from *Gardenia jasminoides* J. Ellis

Continuation of table 2

[69]	Activating AMPK-mTORC1 signaling pathway to initiate autophagy and improving the Beclin 1/Bcl-2 interaction by regulating their phosphorylation to prevent further autophagy	Solution	Experimental (*in vitro*)	Orientin derived from *Polygonum orientale L.*
[70]	Decreasing fibrosis, oxidative stress, inflammatory response, and hypoxia induce cardiomyocyte apoptosis and activating the eNOS/NO signaling cascades	Solution	Experimental (*in vitro and in vivo*)	Orientin
[71]	Alkaloeid compound increasing cell viability	Extract	Experimental (*in vitro*)	hexahydrobenzo[c] phenanthridine alkaloids derived from *Corydais ambigua* var. *amurensis*
[72]	Protective effects toward H9c2 cells injury by increasing cell viability	Extract	Experimental (*in vitro*)	C21 steroidal glycosides derived from *Cynanchum stauntonii*
[73]	Decreasing apoptosis and inhibited the activities of renin and angiotensin-converting enzyme and reducing the expression of angiotensin	Extract	Experimental (*in vitro and in vivo*)	Trans-polydatin derived from *polygonum cuspidatum*
[74]	Diminishing the protein level of cleaved caspase-3, LC3-II, Beclin1 and Sirt1 and suppressing autophagy and apopotosis	Extract	Experimental (*in vitro*)	Coptisine derived from *Rhizoma coptidis*
[75]	Up-regulation of autophagy and enhancement of mitochondrial biogenesis via Sirt3 activity	Solution	Experimental (*in vitro and in vivo*)	Polyphenolic derived from *Polygonum cuspidatum*
[76]	Increasing pyruvate dehydrogenase-mediated aerobic metabolism and restoration of aerobic glucose oxidation	Solution	Experimental (*in vitro*)	*Panax notoginseng* saponin derived from *Panax notoginseng*
[77]	Enhancement of autophagic flux and removal of dysfunction of mitochondria	Solution	Experimental (*in vitro and in vivo*)	Gastrodin derived from *Gastrodia elata*
[78]	Reducing oxidative stress and apoptosis via affecting ERα and GPR30 to activation PI3K pathway and its downstream apoptosis proteins	Solution	Experimental (*in vitro*)	Notoginsenoside R1 derived from *Panax notoginsenosides*
[79]	Regulation of mitochondrial pathway (mediated by 14-3-3η signaling pathway)	Solution	Experimental (*in vitro*)	Luteoloside derived from several Chinese medicines
[80]	Down-regulating miR-22 expression and activating the PI3K/AKT and JAK1/STAT3 pathways and reduced apoptosis	Solution	Experimental (*in vitro*)	*Angelica sinensis* polysaccharide
[81]	Recovering the Activated Peroxisome Proliferator- Receptor-γ (PPAR- γ) and eNOS pathway activity and reduced apoptosis and inflammatory response	Solution	Experimental (*in vitro*)	Emodin derived from *Rheum palmatum L.*
[82]	Attenuating oxidative abnormalities and modulating the antiapoptotic proteins.	Methanolic extract	Experimental (*in vitro*)	Rutin derived from *Spermococe hispida*
[83]	Restoration autophagic flux via activation of PI3K/Akt/mTOR signaling pathway	Ethanolic extract	Experimental (*in vitro and in vivo*)	Lactone derived from *Ligusticum chuanxiong*
[84]	Rising cellular antioxidant defense capacity via inducing the phosphorylation of AKT and subsequently activating the Nrf2/HO-1 signaling pathway	Solution	Experimental (*in vitro and in vivo*)	Total flavonoids derived from *Clinopodium chinense*

Continuation of table 2

[85]	Inhibiting self-cleavage of OMA1, causing to attenuate OPA1 cleavage and reducing apoptosis	Solution	Experimental (*in vitro*)	Epigallocatechin gallate derived from *Camellia sinensis*
[86]	Inhibiting PI3K/AKT-mediated ER stress, apoptosis and oxidative stress	Solution	Experimental (*in vitro and ex vivo*)	Tournefolic acid B derived from *Clinopodium chinense*

Medicinal plants and their derivatives analyzed in Table 2 provide their cardioprotective effects through several mechanisms, such as follows.

Antioxidant activity. Oxidative stress and ROS have been proven to be a potent inducer of oxidative injury, programmed cell death i.e. apoptosis [87]. ROS, which have highly toxic and reactive properties, generated due to ischaemia and augment the degree of myocardial damage sustained by the ischaemic myocardium. To cope with these toxic agents humans developed a natural defense system. The defense mechanisms include enzymes, such as SOD, GPX, CAT, guaiacol peroxidase (POX), peroxiredoxins (Prxs), ascorbate-glutathione (AsA-GSH), ascorbate peroxidase (APX), monodehydroascorbate reductase (MDAR), dehydroascorbate reductase (DHAR) and glutathione reductase (GR) [88]. Another cardioprotective mechanism is preventing myocardial injury via regulation or or activation of pathways that contribute to antioxidant activity. For instance, herbal compounds regulatied Nox/NF-κB/AP1 pathway, which causes nonmitochondrial cellular ROS and inflammatory cytokines generation through the multiple signal pathways [66]. Another antioxidant pathway is activation of eNOS. Phytochemicals can increase NO production in heart and inhibit superoxide by quenching it [70]. Also activation of PI3 K/Akt signaling pathway can suppress mitochondrial-dependent apoptosis and oxidative stress, by activating HO-1 and NQO1, which are Nrf2 mediated-antioxidants [21; 84]. Under pathological conditions, for instance, myocardium infraction and stroke, this defense system is disrupted. Consequently, generation of free radicals increases and the scavenging effects of antioxidants, leading to oxidative damage to cardiomyocytes. Medicinal herbs contain polyphenols that attenuate the level of oxidizing agents and can directly scavenge hydrogen peroxide, superoxide and hydroxyl radicals, increasing the cardiomyocytes viability and reducing the infarct size [14].

Anti-apoptotic properties. ROS induces cell dysfunction and cardiomyocytes necrosis via other mechanisms. They stimulate and activate calpains and metalloproteinases, mitochondrial permeability transition pore (MPTP) opening which cause to swelling and lysis of cardiomyocytes. This process may cause release of pro-apoptotic factors in the cytosol, so this mechanism is contributing to cell death [89]. Hence, another cardioprotective mechanism of medicinal plants and their derivatives is regulating pro-apoptotic genes in cardiomyocytes hypoxic condition. They can down-regulating gene expression levels of pro-apoptotic genes such as Bax, Fas, caspase-3 and caspase-9 proteins. In addition they can up-regulating Bcl-2 and Bcl-xl proteins [51; 54; 57]. Another protective mechanism is prevented a reduction in cell viability, decreased the amount of lactate dehydrogenase (LDH) activity release, which is used as indicators of cardiomyocyte injury and improved cell viability [57]. Also they can protect cardiomyocytes against hypoxia via suppress multiple signaling pathways such as PKC epsilon/mK ATP and redox-sensitive ERK/Nrf2 and TLR4/NF-κB pathways, which attributed ROS arising from CYP-catalyzed processes and apoptosis trigger [23; 57]. They also can suppress apoptosis through activating the AMPK, PI3K/Akt/eNOS, GLP-1R, PI3K/AKT, JAK1/STAT3 and Akt/GSK-3β signaling pathways that plays important roles in cell survival and apoptosis [13; 33; 67; 68; 80] and regulating Akt/Nrf2/HO-1 signaling. Up-regulation of eNOS can protect against myocardial infarction injury via suppressing vascular cell adhesion molecule expression and preventing excessive leukocyte tissue infiltration. In addition phytochemicals increasing hemeoxygenase-1 (HO-1), which is an inducible enzyme with potent antioxidant activity [32]. Thus, phytochemicals up-regulating MAPK ERK1/2 pathway and modulating the PI3K/Akt pathway and reduced apoptosis in cardiomyocytes [55; 58]. Besides, phytochemical prevented cytochrome c release to protect cardiomyocytes from apoptosis via activation some pathways [85].

Reducing the calcium influx. During the acute myocardial ischemia, results in reduction of ATP production and cell metabolism switch to anaerobic

glycolysis due to lack of oxygen. It can cause a drop in intracellular pH and the production of lactate. This induces ion pump function unbalance and the Na^+-H^+ exchanger to extrude H+ and causes in intracellular Na+ accumulation, which activates the $2Na^+$-Ca^{2+} exchanger to function in inverse to throw out Na+ and results intracellular Ca^{2+} overload [4]. Polyphenols, such as flavonoids components, inhibited [$Ca^{(2+)}$] i contents in cardiac muscle cells and prevented the changes induced by KCl in cardiac myocytes and K-ATP channel-opening in the cardiac myocytes has been may attributed to reduced Ca^{2+} influx. They can consequently prolong hypoxia endurance time in cardiac myocytes [17; 56]. Besides in molecule assay, they reduced sensitivity to Ca^{2+}-induced mitochondrial permeability transition (MPT) pore opening and reduced necrotic and apoptotic cell death in hypoxic/reoxygenated cardiac myocytes [23]. Also medicinal plants suppress increased in the late sodium current (INaL) that induce intracellular Na(+) overload and finally intracellular $Ca^{(2+)}$ overload through activated reverse $Na^{(+)}$ – $Ca^{(2+)}$ exchange [35].

Antiinflammatory properties. After cardiac reperfusion, inflammatory cascade is triggered and a lot of amounts of pro-inflammatory cytokines like TNF-alpha, IL-1beta, IL-6, and IL-8 are produced and released. These cytokines as main factors in cardiac dysfunction activate neutrophils and endothelial cells and exacerbate myocardial ischemic injury [90]. Therefore inflammation is a detrimental factor in myocyte hypoxia. It has been proven that TLR2 and TLR4 are expressed in cardiomyocytes during myocardial infarction injury and their stimulation by local endogenous ligands results to the up-regulation of their own expression. These two toll-like receptors are mediate to inflammatory receptors. Some medicinal derivatives can attenuate hypoxia–reoxygenation-induced inflammation, via extracellular signal-regulated kinase 1 or 2 (ERK1/2) and c-Jun NH2-terminal kinase (JNK) signaling pathways [60]. ROS generation during hypoxia causes inflammatory responses that activate including the expression of COX-2 and intercellular adhesion molecule1 (ICAM-1), which plays a pivotal role in the linkage between inflammation and apoptosis [91]. Inhibitory effect of medicinal plants on expression of inflammatory neutrophils or gene response and consequently this property can increase cell viability and reduce necrosis volume [57; 64]. One of these related mechanisms is decreasing peroxidase enzyme like MPO, which has both oxidative and inflammatory effects in cardiomyocytes [38]. MPO is an inflammatory marker, elevated in ischemic cases [92]; so inhibiting that is one of the anti inflammatory effects of medicinal herbs. HIF-1 α is known as principal regulator of the molecular hypoxic response and has regulator effect on the cellular and systemic homeostatic responses to hypoxic circumstances by activating the transcription of several genes, consisting those involved in energy metabolism, apoptosis, angiogenesis, other genes, the protein products of which augment oxygen delivery or assist metabolic adaptation to hypoxia [93]. HIF-1 α has a vital role in triggering cellular protection and metabolic alterations in response to oxygen deprivation during myocardial ischemia and adaptive response to cell ischemia and hypoxia [94].

Some herbal compounds can attenuate myocardial ischemia reperfusion injury by up-regulating HIF-1 α expression which transmits a survival signal to the myocardium [62]. For example, promoting HIF-1α expression causes the inhibition of ROS generation, maintenance of mitochondrial membrane potential (MMP) and reduction of calcium influx, so inhibiting the mitochondrial-mediated apoptosis in hypoxic cardiomyocytes [67]. Even so, some studies reported that HIF-1 is negatively attributed to bcl-2 expression and enhancement apoptosis [33; 95]. Several plants can implement their cardioprotective effects by decreasing HIF-1α expression after several weeks [33].

The role of autophagy in myocardial hypoxic injury is still controversial. It is believed that cardiomyocyte necrosis may occur via autophagy up-regulation and through excessive degradation of the necessary cellular components and self-digestion after hypoxia/reoxygenation or ischemic injury [96]. Medicinal plants active compounds can act as the inhibitor of autolysosome, suggesting that they may inhibit autophagosome generation that consequently enhanced cell viability and decreased apoptosis [36; 74]. However some studies indicate that medicinal plants and their derivatives insert their protective effects through up-regulating autophagy along with enhanced autophagic flux via the activation of various pathways [27; 77; 83]. Clearly, autophagy is dysregulated in the process of myocardial hypoxia injury and herbal compounds can restore unbalance in autophagy process and regulating phosphorylation to prevent excessive autophagy.

Conclusion

It should be noted that plant and their derivatives are not always beneficial and their misuse can lead to irreparable complications. For instance, application of methylcysteine, derived from *Allium sativum*

in mice caused toxic effects to the heart. High dose consumption of this compound causes up-regulation of apoptotic genes (Bax and caspase3), hypoxia inducible factor 1 alpha (HIF1a) and down-regulation of the anti-apoptotic marker, Bcl2. It causes hypoxia induced cardiomyocyte apoptosis attributed by engulfment of mitochondria by nucleus [97]. Most of the reviewed studies were carried out on animal hypoxic or ischemic models and on H9c2 cells; so they cannot be generalized in human and it was one of the main limitations of the studies. Medicinal herbs can be used as an effective treatment against myocardial hypoxia mainly through antioxidant, anti apoptosis, anti-inflammatory properties, inhibiting calcium accumulation, HIF-1 α signaling regulation and autophagy regulation. Post-ischemia and chronic treatment of cardioprotection maybe consider as a therapeutic strategies than short term and pre-treatment methods in clinical setting. More clinical trial studies are required in order to obtain more reliable results.

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