ABSTRACT

The recent studies showed that many plants possessed cardiovascular effects. This review was designed to cover the cardiac, cardioprotective, vascular effects of medicinal plants and plants affected blood pressure.

Keywords: Medicinal Plants, Cardiac, Cardioprotective, Vascular, Hypolipidemic, Anti platelet aggregating, Antioxidant.

INTRODUCTION

Plants are a valuable source of a wide range of secondary metabolites, which are used for treatment and prevention of diseases. In some cases, the active principles of plant-derived products have been isolated and characterized, and their mechanisms of action are understood. The recent studies showed that many plants contain ingredients possessed cardiovascular effects [1-46]. This review was designed to cover the cardiac, cardioprotective, vascular effects of medicinal plants and plants affected blood pressure.

Plants with cardiac effects

Achillea santolina

On isolated heart of rats as an experimental model to determine the effect of the methanol extract of Achillea santolina on the electrophysiological properties, the methanolic extract of Achillea santolina induced significant depression of WBCL, AVCT and ERP and non-significant increase in the time constant of recovery (t.rec). It may be considered a potential drug for anti-arrhythmic effect for suppression or treating supraventricular tachyarrhythmia[47].

Adonis vernalis

Strophanthidin aglycone is one of several cardenolides extracted from Adonisvernalis. The direct effect elicited by these compounds is similar to other cardiac glycoside-containing plants and is due to inhibition of the sodium potassium adenosine triphosphatase enzyme system pump. They increase vagal tone, which decreases the rate of sinoatrial node depolarization. In intoxication, the electrocardiographic changes seen are include bradycardia, varying levels of atrioventricular block, ventricular arrhythmias, and ventricular fibrillation [48-49].

Tincture of Adonis vernalis is used by homeopathic physicians in patients suffering from congestive cardiac failure. Its action was very much similar to digitalis on heart. Aqueous extract of Adonis vernalis was found to have cardiac stimulant action on isolated heart preparations. It showed protection against heart failure produced by excessive load and high potassium concentration. Tincture of Adonis vernalis was found to cause cardiac depression which was not blocked by the atropine. In isolated guinea pig and rabbit auricles the drug increased the threshold of electrical stimulation. The dog blood pressure responses was varied with dose, low doses showed rise in blood pressure whereas larger doses showed fall in blood pressure [50].
**Alhagi maurorum**

In evaluation the effect of the ethanolic extract (EE) of *Alhagi maurorum* powdered roots in anaesthetized rats, the results revealed that the extract at a dose of 1 g/kg induced bradycardia only and not myocardial depressant. Glyceryl-n-tetracosan-17-ol-1-oate (a new aliphatic ester isolated from the root of the plant) possessed a heart rate stimulant action and a myocardial depressant action on rat isolated heart [51].

**Althaea rosea**

Alcoholic extract of the flower of *Althaea rosea* (L.) increased the outflow of coronary artery of isolated guinea pig's heart and markedly dilated the blood vessels in the hind-limbs of rats. The extract showed a transient hypotensive effect on anesthetic cats. It inhibited platelet aggregation induced by ADP and showed a inhibitory effect on experimental thrombosis formation [52].

**Ammi visnaga**

*Ammi visnaga* induced relaxation of smooth muscle, including that of the ureter and coronary arteries, in a variety of animal species [53]. Durate et al found that visnadin caused nonspecific inhibition of vascular smooth muscle. It was selectively inhibited the contractile response in the rat isolated aortic ring and portal vein segment. On the other hand, intravenous administration of visnagin decreased blood pressure with no significant changes on the heart rate [54-56]. A chloroform, and methanol extract (1mg/ml) of the fruits inhibited the potassium chloride induced contractions of the rabbit guinea-pig aorta in vitro [57-58]. Visnadin, 60.0 μg/ml or 120.0 μg/ml, increased coronary blood flow in isolated guinea-pig hearts by 46% and 57% respectively [59]. Samidin and khellol glucoside induced positive inotropic effects on heart [60].

In coronary vasospasm and myocardial ischaemia induced by dogs by intramuscular injections of vasopressin, visnadin, dihydrosamidin, khellin and samidin effectively normalized the electrocardiogram when given in a dose of 4.7 mg/kg bw per day intramuscularly for 7 days [60]. Immediately after the rapid intravenous administration of 20-30 mg of khellin to the dogs, the blood pressure drops to about 50 mm Hg., the heart beats considerably slower, and the respiration is momentarily arrested. The entire effect lasts for only a short time, within a minute or two [61]. According to the results obtained by different researchers, khella seems to improve blood supply to smooth muscles and makes myocardial metabolism more efficient. It dilated the coronary vessels, and increased the capacity of the heart without increasing the heat rate or affecting blood pressure [62].

A clinical trial of khellin in 38 cases of angina pectoris and in 8 cases of coronary thrombosis was performed. Continuous treatment, by the oral or intramuscular routes or by both, gave favourable results in 35 out of 38 cases of angina pectoris. Continuously administration of khellin for several weeks to eight patients after coronary thrombosis appeared favourable [60].

**Anchusa strigosa**

The extract was found to have slight inhibitory effect on the auricular contraction in bilaterally vagotomised dog but there was no effect on ventricular contraction in this animal. These results indicate that the site of action is probably blood vessel [63].

**Asclepias curassavica**

Previous studies recorded a positive inotropic activity for asclepin extracted from *Asclepias curassavica*; it was more potent, and safer than other cardiac glycosides (including digoxin). It showed longer duration of action than digoxin (96 h in cat, as opposed to the 72 h of digoxin) [64].

In sheep and guinea-pigs the plant extracts, purified cardenolide, and digoxin exhibited similar toxicity and gross pathology. In a 3 month toxicity study in rats, asclepin was found safe in doses of 0.8, 8, and 20 mg/kg. Cat studies showed that, it less cumulative compared to digoxin. Extracts of *Asclepias curassavica* stimulated mammalian CNS, increasing noradrenaline and serotonin. LD₅₀ of cardenolide was = <50 mg/kg ip in mice [65-66].

**Bacopa monnieri**

Ethanolic extract of whole plant of *Bacopa monnieri* has shown cardiac depressive activity on left ventricular contractility, heart rate and coronary flow in isolated rabbit heart and it appeared that, the activity of ethanolic *Bacopa monnieri* extract was similar to that of quinidine heart [67].

**Brassica nigra**

The local action of mustard may stimulate the cardiac and respiratory activity in sufficient force to arouse one from an attack of fainting. Both the breathing and circulation are stimulated by its reflex action upon the respiratory centers and the heart [68].

**Bryophyllum calycinum**

The aqueous and methanolic leaf extracts decreased arterial blood pressures and heart rates of anaesthetized normotensive and hypertensive rats [54]. The effects of aqueous and methanolic leaf extracts of the herb were examined on arterial blood pressures and heart rates of normal (normotensive) and spontaneously hypertensive rats, using invasive and non-invasive techniques. Both the aqueous and methanolic leaf extracts of the plant (50-800 mg/kg iv or ip) produced dose-related, significant (P<0.05 - 0.001) decreases in arterial blood...
pressures and heart rates of anaesthetized normotensive and hypertensive rats. The hypotensive effects of the leaf extracts were more pronounced in the hypertensive than in normotensive rats. The leaf extracts (0.25 - 5.0 mg/ml) also produced dose-dependent significant (P<0.05 -0.001) decreases in the rate and force of contractions of guinea-pig isolated atria, and inhibited provoked electrical field stimulation (ES-provoked), as well as potassium and receptor-mediated agonist drugs-induced contractions of the rat isolated thoracic aortic strips in a non-specific manner. The inhibitory effects of the leaf extracts on the cardiovascular system of the laboratory animals were resistant to physiological doses of standard antagonist drugs [69-70].

**Caesalpinia crista**

The alcoholic and aqueous extract of *Caesalpinia crista* was evaluated for protection against isoproterenol (85 mg/kg bw) induced myocardial infarction in albino rats. The heart damage induced by isoproterenol was indicated by elevated levels of the marker enzymes such as creatine kinase-isoenzyme, lactate dehydrogenase, serum glutamate oxaloacetic transaminase and serum glutamate pyruvate transaminase in serum with increased lipid peroxide and reduced glutathione content in heart homogenates. Pretreatment with an ethanolic and aqueous extract of *Caesalpinia crista* at a dose of 400 mg/kg, orally for 30 days, reduced significantly (p<0.01) the elevated marker enzyme levels in serum and heart homogenates in isoproterenol - induced myocardial infarction. Histopathological observation revealed a marked protection by the extract in myocardial necrotic damage [71].

**Calendula officinalis**

Calendulozide B-trioside isolated from rhizomes of *Calendula officinalis* didn’t have cardiovascular effects, didn’t affected the tone of intestinal smooth muscles, didn’t affected the diuretic renal function and electrolytes excretion in urine and didn’t affected the biligenic function of the liver. It was devoid of locally irritation properties, but with low hemolytic activity (15000 after Kofler) and an insignificant toxicity both with its one-time and chronic administration [72].

The cardioprotective effect of *Calendula officinalis* in ischemic heart disease was evaluated. The treated rat hearts were perfused with calendula solution at 50 mM in KHB buffer (in mM: sodium chloride 118, potassium chloride 4,7, calcium chloride 1,7, sodium bicarbonate 25, potassium biphosphate 0.36, magnesium sulfate 1.2, and glucose 10) for 15 min prior to subjecting the heart to ischemia, while the control group was perfused with the buffer only. Calendula achieved cardioprotection by stimulating left ventricular developed pressure and aortic flow as well as by reducing myocardial infarct size and cardiomyocyte apoptosis. Cardioprotection appears to be achieved by changing ischemia reperfusion-mediated death signal into a survival signal by modulating antioxidant and anti-inflammatory pathways as evidenced by the activation of Akt and Bcl2 and depression of TNFα [73].

**Calotropis procera**

Latex of *Calotropis procera* was evaluated for protection against isoproterenol (20 mg/100g) induced myocardial infarction in albino rats. The pretreatment with an ethanolic latex extract of *Calotropis procera* at a dose of 300 mg/kg body weight orally three times a day for 30 days, reduced significantly (p<0.01) the elevated markers enzyme levels in serum and heart homogenates in isoproterenol induced myocardial infarction [74].

The effects of ethanol, n-butanol, and ethyl acetate (EtOAc) extracts of the aerial parts of the plant, were evaluated on isolated toad heart. Their mechanisms of action were also studied. Perfusion with 2 μg/ml ethanol, 0.2 μg/mL butanol, and 0.2 μg/mL EtOAc extracts caused a significant decrease in heart rate (bradycardia), significant increase in the force of ventricular contraction, and increase in T-wave amplitude. The different extracts and latex of *C. procera* induced negative chronotropism and positive inotropism on isolated toad heart [75].

**Carthamus tinctorius**

The anti-myocardial ischemia effects of a purified extract of *C. tinctorius* (ECT) was studied both *in vivo* and *in vitro*. An animal model of myocardial ischemia injury was induced by left anterior descending coronary artery occlusion in adult rats. Pretreatment with ECT (100, 200, 400, 600 mg/kg body wt.) protected the heart from ischemia injury by limiting infarct size and improving cardiac function. In the *in vitro* experiment, neonatal rat ventricular myocytes were incubated to test the direct cytoprotective effect of ECT against H2O2 exposure. Pretreatment with 100-400 microg/ml ECT prior to H2O2 exposure significantly increased cell viability as revealed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. ECT also markedly attenuated H2O2-induced cardiomyocyte apoptosis, as detected by Annexin V and PI double labeling with flow cytometry. ECT pretreatment significantly inhibited H2O2-induced ROS increase. The cardioprotective effects of ECT in myocardial ischemia operate partially through reducing oxidative stress induced damage and apoptosis. The protection is achieved by scavenging of ROS and modulating the PI3K signaling pathway [76].

The protective effects of *Carthamus tinctorius* injection (CTI) (2.5 and 0.625 g/kg, respectively, ip for 5 days) on isoprenaline-induced acute myocardial ischemia (AMI) was evaluated in rats, the underlying mechanisms were also studied. Results showed that CTI (2.5 and 0.625 g/kg) significantly inhibited the typical ECG S-T segment elevation, reduced concentration...
of IL-6 and TNF-α in serum, suppressed overexpression of Bax protein and also inhibited the reduction of Bcl-2 expression and markedly depressed the Bax/Bcl-2 ratio. These findings demonstrate that CTI is cardioprotective against AMI in rats and is likely to related to decrease inflammatory response mediated by TNF-α and IL-6, down-regulate protein level of Bax and up-regulate that of Bcl-2 in the heart tissue [77].

The effects of safflower injection (SI) in protecting heart, on energy charge and anti-apoptosis gen bcl-2 in cardiac tissue were investigated by Rats’ Langendorff isolated heart infused model. As compared with the control, SI improved the functions of cardiac contraction and dilation, increasing coronary blood flow, and strengthening the bcl-2 protein expression [78].

The protective effects of N-[(p-Coumaroyl)serotonin (C) and N-feruoylserotonin (F) were investigated in perfused guinea-pig Langendorff hearts subjected to ischemia and reperfusion. Changes in cellular levels of high phosphorysorous energy, NO and Ca2+ in the heart together with simultaneous recordings of left ventricular developed pressure (LVDP) were monitored by nitric oxide (NO) electrode, fluorometry and 31P-NMR. The rate of recovery of LVDP from ischemia by reperfusion was 30.8% in the control, while in the presence of C or F a gradual increase to 63.2 or 61.0% was observed. Changes of transient NO signals (TNO) released from heart tissue in one contraction (LVDP) was observed to be upside-down with respect to transient fura-2-Ca2+ signals (TCa) and transient O2 signals detected with a pO2 electrode. At the final stage of ischemia, the intracellular concentration of Ca2+ and the release of NO increased with no twitching and remained at a high steady level. The addition of C increased the NO level at the end of ischemia compared with the control, but Ca2+ during ischemia decreased. On reperfusion, the increased diastolic level of TCa and TNO returned rapidly to the control level with the recovery of LVDP. By in vitro EPR, C and F were found to directly quench the activity of active radicals. Accordingly, the antioxidant effects of both derivatives isolated from safflower play an important role in ischemia-reperfusion hearts in close relation with NO [79].

The effects of Flos Carthami FC(EtOH)) ethanolic extract on LPS-induced apoptosis in H9c2 cardiomyoblast cells was studied. FC(EtOH) (62.5 microg/mL) inhibited LPS-induced apoptosis by suppressing JNK1/2 activity, which resulted in the reduction of both IkappaB degradation and NF kappaB activation. In addition, FC(EtOH) led to activation of anti-apoptotic proteins, Bcl-2 and Bcl-XL, the stabilization of the mitochondria membrane and the down-regulation of extrinsic and intrinsic pro-apoptotic proteins, such as TNF alpha, active caspase-8, t-Bid, Bax, active caspases-9, and -3. The ability of Carthamus tinctorius to suppress JNK activity and inhibit LPS-induced TNF alpha activation and apoptosis in H9c2 cardiomyoblast cells could potentially serve as a cardio-protective agent against LPS-induced apoptosis [80].

The effects of safflor yellow A (SYA) was evaluated on cultured rat cardiomyocytes exposed to anoxia/reoxygenation (A/R). The A/R exposure markedly decreased the viability of cardiomyocytes, suppressed the activities of SOD, GSH, CAT, GSH-Px, and Bcl-2 protein expression. Meanwhile, the A/R exposure markedly increased the release of LDH, CK, MDA production in the cardiomyocytes, increased the rate of apoptosis, caspase 3 activity and Bax protein expression. Pretreatment with SYA (40, 60 and 80 nmol/l) concentration-dependently blocked the A/R-induced changes in the cardiomyocytes. Pretreatment of the cardiomyocytes with the SYA (80 nmol/l) produced protective effects that were comparable to those caused by N-acetylcysteine (NAC, 200 µmol/l) [81].

The effects and the proper dosage of Panax notoginseng (EPN) combined with Carthamus tinctorius (ECT) to strengthen their cardio-protective effects were investigated. Meanwhile, their potential anti-oxidative stress and anti-inflammation effect were assessed. Rats were orally given individual EPN 50, 100mg/kg, ECT 100, 200mg/kg, and different combinations between them. Myocardial infarction was produced by occlusion of the left anterior descending coronary artery for 24h. Infarct area was determined with 2,3,5-triphenyltetrazolium chloride (TTC) staining. The biomarkers related to myocardial ischemia injury were determined. Simultaneously, hemodynamic parameters were monitored as left ventricular systolic pressure (LVSP), LV end-diastolic pressure (LVEDP) and maximal rate of increase and decrease of left ventricular pressure (dP/dt(max)). The oxidative stress indicators and inflammatory factors were also evaluated. The results showed that EPN or ECT significantly reduced infarct size, improved cardiac function, decreased levels of creatine kinase (CK) and lactate dehydrogenase (LDH) (all P<0.05 vs. control ). EPN or ECT alone also restrained the oxidative stress related to myocardial ischemia injury as evidenced by decreased malondialdehyde (MDA) and elevated superoxide dismutase (SOD) activity (all P<0.05 vs. control). However, this cardio-protective effect was further strengthened by their combinations. Among all the combinations, EPN 50mg/kg plus ECT 200mg/kg showed predominant potential to reduce infarct size (22.21±1.72%, P<0.05 vs. each single, respectively), preserve cardiac function (P<0.05 vs. ECT 200mg/kg for LVEDP and -dP/dt(max)) after myocardial ischemia injury in rats. This heart protection was confirmed with the lowered cardiac troponin I (cTnl) (P<0.05 vs. ECT 200mg/kg and EPN 50mg/kg, respectively). EPN 50mg/kg plus ECT 200mg/kg markedly increased SOD and GSH-Px activity (475.30±23.60U/ml, P<0.05 vs. each single, respectively), while elevated MDA level was significantly depressed.
Meanwhile, the inflammatory cascade was inhibited as evidenced by decreased cytokines such as tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and interleukin-1β (IL-1β) [82].

The protective effect of safflower yellow B (SYB) was investigated against vascular endothelial cells (VECs) injury induced by angiotensin-II (Ang-II). Comparing with control group, Ang-II was able to increase Ca$^{2+}$ and ROS level, decrease MMP level, inhibit complex IV activity and enhance caspase 3 activity in VECs, as a result, enhance apoptosis of VECs. SYB was able to eliminate the effect of Ang-II on VECs via regulating Ca$^{2+}$, mitochondrial structure and function and inhibiting apoptosis[83].

**Cheiranthus cheiri**

Previous study showed that cardiac glycosides called cheiranthosides I-XI together with two olitoriside and erysimoside were isolated from the seeds of the plant.

The glycosides were evaluated for their inhibitory activity against Na$^+$,K$^+$ -ATPase by comparing with typical cardiac glycosides. Two of them, cheiranthoside III and VIII, showed high inhibiting activity which was equivalent to that of digitoxin. Cheiranthoside XI containing a rhamnopyranosyl digitoxopyranosyl moiety and a carboxyl group showed the lowest activity which was similar to that of the inactive aglycone, strophanthidin [84].

**Plant affected blood pressure and vascular tone**

**Agrimonia eupatoria**

A hypotensive effect in anaesthetised cats has been documented for an agrimony extract given by intravenous injection; blood pressure was lowered by more than 40% [85].

**Agropyron repens**

The sugar mannitol present in large quantities in this herb, and is known as a standard ‘osmotic diuretic’, that is, it is absorbed whole from the gut and excreted largely by the kidney tubules. Its presence in the tubules means that extra water has to be retained in order to maintain osmotic pressure. The saponins and vanillin, also have diuretic properties. Because of Couch grass diuretic and antimicrobial effects, it was used to flush out the urinary tract during infections [86].

**Alhagi maurorum**

The diuretic effects of methanol extracts of *Alhagi maurorum* was evaluated in a single or repeated (1 x 5days) oral dose of 500 or 1000 mg/ kg orally in albino rats, compared to furosemide 20 mg/ kg. Repeated oral administration of *Alhagi maurorum* in doses of 500or 1000 mg/kg significantly (P < 0.05) increased urine volume and the sodium and potassium excretion rate. The authors concluded that methanol extracts of *Alhagi maurorum* have a significant diuretic, kaluretic and saluretic effect [87].

The diuretic effects of a distilled product of *Alhagi maurorum* was investigated in goat. Results of oral distilled product of Alhagi showed that the level of urine specific gravity was decreased. Also, It was shown that the pH was decreased insignificantly. Concentrations of Na and Cl were increased in urine following consumption of distilled product of Alhagi at doses (8, 16 ml/kg) (P < .05). These effects were marked at 180 and 120 minutes. Concentrations of urine K and Ca were decreased in urine following oral consumption of distilled product of Alhagi at doses 8, 16 ml/kg (P < .05). Concentration of urine creatinine was decreased significantly (P < .05) [88].

**Allium sativum**

Experimental and clinical studies showed that garlic produced hypotensive effects. Garlic induced significant reduction in systolic and diastolic blood pressure. The authors postulated that the hypotensive action of garlic is due to a direct relaxant effect on smooth muscles[89-97].

**Anchusa strigosa**

The aqueous extract of *A. strigosa* (100 to 200 mg/kg, iv) in anaesthetised dogs produced hypotensive effect for more than half an hour after an initial transient rise. The hypotensive effect was not blocked by atropine or mepyramine maleate. The extract failed to modify the effect of acetylcholine, histamine or epinephrine. Its effect was not altered in spinal dogs. The extract has no significant effect on isolated frog heart [63].

**Anethum graveolens**

Intravenous administration of 12.5 mg/kg body weight of 70% dried ethanol extract of the fruits dissolved in normal saline or 4.0 μl/kg body weight of the essential oil induced diuresis and enhance sodium and calcium excretion in dogs [98]. Intravenous administration of 5–10 mg/kg body weight of 5% seed oil in saline to cats caused hypotension and increased respiration volume[99, 100].

**Anthemis nobelis**

The hypotensive effect of *Chamaemelum nobile* aqueous extract (CNAE) in spontaneously hypertensive was studied in rats. Single oral administration of CNAE (140 mg/kg) produced a significant reduction (p < 0.05) in systolic blood pressure (SBP) after 24 h of the administration. Daily oral administration of CNAE (140 mg/kg) during 3 weeks produced a significant reduction in SBP in the day 8 (p < 0.01) of treatment. Furthermore, CNAE produce a significant increase in urinary output and electrolytes excretion (p < 0.01) from the day 8 to the end of treatment. The in vitro vasorelaxant effect of *C. nobile* aqueous extract was evaluated using aortic ring
isolated from Wistar rats. *C. nobile* aqueous extract at doses of 5, 10 and 20 mg/ml possessed in vitro vasorelaxant effect. Incubation of aqueous *C. nobile* extract for 30 minutes produced a significant shift of the dose-response curve to norepinephrine (NE) (10⁻⁸ to 10⁻⁷) M (p < 0.001) [101].

**Apium graveolens**

The effects of aqueous and ethanol extracts of *Apium graveolens* (0.5-15 mg/kg) was investigated on the mean blood pressure of anaesthetized rabbits and contractility of isolated atria of the rats. The intravenous administration of aqueous extracts induced the least hypotensive effects (14.35±2.94%), while the ethanol extract caused the greatest fall in the blood pressure (45.79±10.86%). Hypotensive effect of the extracts was partially blocked by atropine (0.3 mg/kg). Both aqueous and ethanol extracts of celery exhibit a negative chronotropic and inotropic actions. Aqueous extract decreased the rate of contractions by 12.88±2.74% and amplitude by 8.73±0.89%. Ethanol extract inhibited the rate of atria contractions by 34.26±5.69% and amplitude by 25.40±3.61%. Pretreatment of rat atria with atropine (1 μM) partially blocked the inhibitory response induced by aqueous and ethanol extracts of *Apium graveolens* [102].

**Arachis hypogaea**

Bioactive peptides with antihypertensive effects against Angiotensin Converting Enzyme were isolated from peanut [103]. The active ingredient of *A. hypogaea* such as resveratrol can act as a sympathomimetic compound, its effects was completely blocked by propranolol (beta blocker) and partially blocked by prazosin (alpha blocker) and were also found to be highly potentiated by reserpine [104].

**Avena sativa**

In addition to cholesterol lowering effect of *Avena sativa*, it improved the blood pressure when consumed with vitamin C, improved endothelial function, and exerted angiotensin converting enzyme inhibition. According to these results, the United States Food and Drug Administration in 1997 approved the heart-health benefit of food containing soluble fiber from oats [105]. Katz *et al.*, reported that a single serving of oatmeal opposed the disturbances in endothelial function observed after the consumption of a high fat meal [106]. In overweight patients, beta glucan from oats has been shown to decrease hypertension. Avenanthramide is an oat polyphenol that has been shown to enhance production of nitric oxide, a potent vasodilator, and to inhibit thickening of vascular smooth muscle. Both actions are preventative to developing atherosclerosis [107-108].

**Bellis perennis**

The effect of *Bellis perennis* on postpartum blood loss was studied by double blind, placebo-controlled, randomized, clinical trial. At 72h postpartum, mean Hb levels remained similar after treatment with homeopathic remedies (12.7 versus 12.4) as compared to a significant decrease in Hb levels in the placebo group (12.7 versus 11.6; p<0.05), in spite of less favorable initial characteristics of the treatment group. The mean difference in Hb levels at 72h postpartum was -0.29 (95% CI -1.09; 0.52) in the treatment group and -1.18 (95% CI -1.82; -0.54) in the placebo group (p<0.05) [109].

**Bryophyllum calycinum**

The aqueous and methanolic leaf extracts decreased arterial blood pressures and heart rates of anaesthetized normotensive and hypertensive rats. The effects of aqueous and methanolic leaf extracts of the herb were examined on arterial blood pressures and heart rates of normal (normotensive) and spontaneously hypertensive rats, using invasive and non-invasive techniques. Both the aqueous and methanolic leaf extracts of the plant (50-800 mg/kg iv or ip) produced dose-related, significant (P<0.05 - 0.001) decreases in arterial blood pressures and heart rates of anaesthetized normotensive and hypertensive rats. The hypotensive effects of the leaf extracts were more pronounced in the hypertensive than in normotensive rats. The leaf extracts (0.25 - 5.0 mg/ml) also produced dose-dependent significant (P<0.05 -0.001) decreases in the rate and force of contractions of guinea-pig isolated atria, and inhibited provoked electrical field stimulation (ES-provoked), as well as potassium and receptor-mediated agonist drugs-induced contractions of the rat isolated thoracic aortic strips in a non-specific manner. The inhibitory effects of the leaf extracts on the cardiovascular system of the laboratory animals were resistant to physiological doses of standard antagonist drugs [69-70].

**Caccinia crassifolia**

A glucoside and its aglucone were isolated from the *plant*. Both compounds exhibited a diuretic action which appeared to be due to an increase in glomerular filtration. The dose which induced diuresis did not have any other significant effects [110].

**Caesalpinia crista**

The administration of aqueous leaf extract of *Caesalpinia crista* induced a progressive decrease of blood pressure. The hypotensive action of the extract was dose-dependent and reversible. Similar results were obtained using acetylcholine. Hypotension induced by aqueous leaf extract of *Caesalpinia crista*, or acetylcholine were inhibited by atropine. On the other hand, it significantly reduced blood pressure caused by the prior administration of adrenaline. These results showed that the leaves of *Caesalpinia crista* exerted hypotensive and antihypertensive effects by different mechanisms [111].

**Capparis spinosa**

The vaso relaxant effect of *Capparis spinosa* aqueous extract (CSAE) at a dose of 10 mg/ml was
studied on the isolated aortic rings of normal rats. Adding of CSAE during the plateau phase of contraction, induced by noradrenaline and KCl, produced a rapid relaxation. Incubation of aortic ring with CSAE during 30 min shifted the noradrenaline induced dose response curve (p<0.001), the maximum response (p<0.001) was attenuated which indicating that antagonistic effect of the α1- adrenoreceptors was non-competitive. However, endothelium remove significantly reduced the vaso relaxant effect of CSAE (p<0.01). Furthermore, nitric oxide inhibition reduced the vaso relaxant effect of CSAE. However, cyclo-oxygenase inhibition did not affect the vaso relaxant effect of CSAE (p<0.05). Inhibition of L-type voltage dependent Ca2+ channels did not reduce the observed CSAE vaso relaxant effect (p<0.05). Accordingly the authors suggested that vasorelaxant effect of (CSAE) may be mediated via an α1-adrenoreceptors antagonism and/or modulation of nitric oxide synthesis [112].

The in vitro vasomotor effects of aqueous extract of different parts of Capparis spinosa (roots, leaves, stems, flowers, fruits and kernels) were evaluated on the rings of thoracic aorta and windpipe of rat. The addition of Capparis spinosa extracts with different concentrations during the stage of contraction led by the phenylephrin for the thoracic arteries showed a light vasodilatation. Another protocol, by incubation 30 min with extracts at different concentrations showed a significant vasodilator effect for fruits and kernels, and vasoconstrictor effect for leaves [113].

Carum carvi
The diuretic activity of Carum carvi was investigated in rats. Water extracts of Carum carvi (100 mg/kg) were administrated orally to male Wistar rats and their urine output was quantitiated at several intervals of time after the dose. After single doses of the extracts of caraway seeds, urine output was significantly increased at all time points, and at 24 h after the dose, the total volume of urine excreted was similar for the plant extracts and furosemide. Carum carvi extracts increased urinary levels of Na+ and K+, while furosemide increased urinary levels of only Na+ and decreased urinary K+. In the 8-day sub-chronic study, Carum carvi extract induced significant diuresis and natriuresis. The plant extracts did not appear to have renal toxicity or any other adverse effects during the study period [114].

Carthamus tinctorius
Safflower yellow (SY) 1-2 g/ kg / day lowered the blood pressure of spontaneously hypertensive rats (SHR), for about 1.86-3.86 kPa. Five weeks after administration of SY, the plasma renin activity and angiotensin II level diminished in the SHR experimental groups, which indicated that the decrease of blood pressure is mediated by inactivation of renin-angiotensin system [117].

To observe the effect of Safflower Injection (SI) on mesenteric microvascular motion in vivo in rabbits, and to explore the effect of nitric oxide (NO) in the process to further investigate the action mechanism of activating blood to remove stasis of SI. The vasomotion was induced by noradrenaline (NA) in vivo, then the changes of vasomotion after injecting SI and N(G)-monomethyl-L-arginine (L-NMMA, a NO synthase inhibitor) were measured. L-NMMA injection alone can inhibit the NA induced vasomotion in vasoconstriction state, while SI injection alone can inhibit it in vasodilation state. SI could abolish the effect of L-NMMA on vasomotion but L-NMMA did not influence the effect of SI on vasomotion [118].

The mechanism of saffor effect on renal ischemia/reperfusion (I/R) injury in rats was studied. After rat's I/R injury model was established and after three treatment doses (high, middle and low doses), renal function was assessed by measuring serum creatinine, blood urea nitrogen, urine osmotic pressure and urine osmotic pressure/blood osmotic pressure. The apoptosis rate in I/R renal tissue was measured by TUNEL method and caspase-3 concentration was measured by immunohistochemistry. Reperfusion of the ischemic kidney induced marked renal dysfunction. Saffor injection significantly inhibited the reperfusion-associated increase in apoptosis rate and caspase-3 protein absorbance value. Moreover, the renal dysfunction at all treatment groups was markedly ameliorated by Saffor injection. (P<0.01). Accordingly, the protective effect of Saffor injection may be related to the inhibition of cell apoptosis and caspase-3 gene expression following renal I/R [119].

The vasodilatation effects of hydroxy-safflor yellow A (HSYA) on pulmonary artery (PA) were explored by an assay of tension study on rat pulmonary artery (PA) rings. Results suggest that HSYA possessed vascular relaxation effects on rat PA by activating the KV channel in pulmonary vascular smooth muscle cells (PVSMCs) [120]. Intravenous injection of the HSYA significantly reduced MAP and HR in both normotensive rats and SHR in a dose-dependent manner. HSYA reduced left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), the maximum rate of increase of left ventricular pressure (+dp/dt(max)) and heart rate (HR) in a dose-dependent manner. HSYA had no remarkable effect on the maximum rate of decrease of left ventricular pressure (-dp/dt(max)); BK(Ca) and K(ATP) blocker can weakened the inhibitory effect of HSYA on heart function and HR, but K(V) and K(ACh) blocker did not significantly weaken the HSYA effects [121].

The therapeutic and preventive effects of Safflower Injection (AI) in vascular crisis after free flap transplantation was studied clinically. Sixty patients
undergoing free flap transplantation were randomly assigned to the treatment group and control group, thirty in each. Free flap transplantation was performed on all patients, and medication was given 0.5h before flap vascular anastomosis, 1-7 days after surgery. Twenty ml Al was intravenously dripped to patients in the treatment group after adding in 250 ml 5% glucose injection, while Dextran-40 was intravenously dripped to patients in the control group. The medication was conducted once per day. The hemorheology and four indices of blood coagulation [prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen] were compared between the two groups before operation (TO), during operation (T1), 24 h after operation (T2), three days after operation (T3), and seven days after operation (T4). Meanwhile, flaps were observed and adverse reaction recorded. The clinical efficacy and safety were compared. Better result was obtained in the treatment group when compared their clinical efficacy (86.67% vs 60.00%, P<0.05). The whole blood high and low viscosity, plasma viscosity, red blood cell volume, RBC aggregation index all decreased, and RBC deformed index increased in the two groups at T4, showing statistical difference when compared with those at T3 (P<0.05, P<0.01). There was no statistical significance in the four indices of blood coagulation when compared with any time point in the same group (P>0.05). There was no statistical significance in hemorheology and the four indices of blood coagulation between the two groups at the same time point (P>0.05). The adverse reaction rate in the treatment group was lower than that in the control group, showing statistical difference (13.33% vs 30.00%, P<0.05) [122].

The vascular effect of N-(p-coumaroyl)serotonin (CS) and N-feruloylserotonin (FS), was evaluated. Both CS and FS (each 10 to 100 μM) relaxed rat femoral arteries, which were pre-contracted by 10⁻⁵ M phenylephrine or 50 mM KCl, independently of their endothelium. Both CS and FS also concentration-dependently inhibited the increase of cytosolic free Ca²⁺ concentration that was induced by KCl or 5-hydroxytryptamine in cultured rat vascular smooth muscle cells (VSMCs). The effects of CS and FS was also examined on platelet-derived growth factor (PDGF)-BB-evoked proliferation and migration of the VSMCs. Both CS and FS inhibited PDGF-BB-evoked proliferation and migration of the VSMCs in a concentration-dependent manner. They also inhibited PDGF-BB-induced phosphorylation of PDGF receptor β and ERK1/2, and Ca²⁺ release from sarcoplasmic reticulum in the VSMCs in a concentration-dependent fashion. These result explain a part of anti-atherogenic mechanism that underlies their ability to improve vascular distensibility and to inhibit aortic hyperplasia [123].

The effects of Safflower (Chinese Traditional Medicine) on the intestine ultrastructure characteristics during intestine ischemia/ reperfusion injury (I/RI) was studied in rabbits. The intestine ultrastructure was badly injured in untreated ischemia/reperfusion group. Mitochondria and intestinal mucosal cells were swollen and endoplasmic reticulum expanded, however, in the Safflower injection group the ultrastructural injury of the ischemia greatly ameliorated [124].

The effects of long-term supplementation with Safflower seed extract (SSE) on arterial stiffness in human subjects were evaluated in a double blind clinical trial. 77 males (35-65 years) and 15 postmenopausal females (55-65 years) with high-normal blood pressure or mild hypertension who were not undergoing treatment received SSE (70 mg/day as serotonin derivatives) or placebo for 12 weeks, and pulse wave measurements, ie, second derivative of photoplethysmogram (SDPTG), augmentation index, and brachial-ankle pulse wave velocity (baPWV) were conducted at baseline, and at weeks 4, 8, and 12. Vascular age estimated by SDPTG aging index, improved in the SSE-supplemented group when compared with the placebo group at four (P=0.0368) and 12 weeks (P=0.0927). The trend of augmentation index reduction (P=0.072 versus baseline) was observed in the SSE-supplemented group, but reduction of baPWV by SSE supplementation was not observed. The SSE-supplemented group also showed a trend towards a lower malondialdehyde-modified-LDL autoantibody titer at 12 weeks from baseline [125].

The effects of defatted safflower seed extract and its phenolic constituents, serotonin derivatives, on atherosclerosis were studied. Ethanol-ethy acetic extract of safflower seeds (SSE) inhibited low-density lipoprotein (LDL) oxidation induced in vitro by an azo-containing free-radical initiator V70 or copper ions. Two serotonin derivatives [N-p-coumaroylserotonin (CS) and N-feruloylserotonin (FS)] and their glucosides were identified as the major phenolic constituents of the extract. The study revealed that a majority of the antioxidative activity of SSE was attributable to the serotonin derivatives. Orally administered CS and FS suppressed CuSO₄-induced plasma oxidation ex vivo. Long-term (15 week) dietary supplementation of SSE (1.0 wt %/wt) and synthetic serotonin derivatives (0.2-0.4%) significantly reduced the atherosclerotic lesion area in the aortic sinus of apolipoprotein E-deficient mice (29.2-79.7% reduction). The plasma level of both lipid peroxides and anti-oxidized LDL autoantibody titers decreased concomitantly with the reduction of lesion formation [126].

The modifying effect of hydroxyasflor yellow A (HSYA) on vascular endothelial cells (EC) induced by hypoxia and its mechanisms were evaluated. HSYA upregulated the bcl-2/bax ratio, which is downregulated under hypoxia, increased VEGF protein concentration and VEGF mRNA expression and enhanced HIF-1 alpha protein accumulation and its transcriptional activity [127].
The mechanism of regulating HIF-1alpha expression by hydroxysafflor yellow A (HSYA) in Eahy 926 cell line under 1% O2 hypoxia was studied. Eahy 926 cells were incubated with HSYA (100, 10 and 1 micromol x l⁻¹) under hypoxia for the indicated time after treatment. HSYA at 100 micromol x l⁻¹ increased Eahy 926 cells proliferation rate under hypoxia. HIF-1alpha mRNA and protein expression were up-regulated in the presence of HSYA. VHL, p53 mRNA and protein expression decreased significantly after 8 hours of treatment under hypoxia. Accordingly, HSYA protected Eahy 926 cells from hypoxia, and up-regulated HIF-1alpha expression partially via its inhibition of VHL and p53 expression [128].

The effect of Safflower injection was evaluated on pulmonary hypertension in rats during chronic hypoxia and hypercapnia. mPAP, weight ratio of right ventricle (RV) to left ventricle plus septum (LV + S) were much higher in rats of hypoxic hypercapnic group than those of control group. The concentration of TXB2 and the ratio of TXB2/6 keto-PGF1a were significantly higher in rats of hypoxic hypercapnic group than those of control group and hypoxic hypercapnia + Safflower injection group. The results of light microscopy showed that WA/TA (vessel wall area/total area), SMC (the density of medial smooth muscle cell) and PAMT (the thickness of medial smooth cell layer) were significantly higher in rats of hypoxic hypercapnic group than those of control group and hypoxic hypercapnia + Safflower injection group. The results of electron microscopy showed proliferation of medial smooth muscle cells and collagen fibers of pulmonary arterioles in rats of hypoxic hypercapnic group, and Safflower injection reversed these changes [129].

The effect of Hydroxysafflor yellow A (HSYA) on human umbilical vein endothelial cells (HUVECs) under hypoxia was investigated. HSYA inhibited cell apoptosis and cell cycle G1 arrest induced by hypoxia. HSYA treatment increased the Bcl-2/Bax ratio of protein and mRNA, reduced p53 protein expression in cell nucleus. In addition, HSYA enhanced the NO content of cell supernatant under hypoxia, accompanied with upregulating eNOS mRNA expression and protein level. The results demonstrate that HSYA could protect HUVECs from hypoxia induced injuries by inhibiting cell apoptosis and cell cycle arrest [130].

Centaura cyanus

The effect of cornflower water extract was compared with hydrochlorothiazide on diuresis, Na⁺ and K⁺ excretion, and the changes in the prostaglandin E2 and kinins levels in the plasma of experimental rat’s plasma. In hydrochlorothiazide receiving rats, the volume of urine excreted two and four hours after the administration of the drug was by 18% and 17%, respectively, higher as compared to the rats that were given cornflower water extract (P<0.05). The diuretic effect of cornflower water extract was noted in the animal group receiving this extract as compared to the control group: after two hours, the volume of urine excreted increased from 2.03±0.03 ml to 2.44±0.04 ml, and after four hours from 3.88±0.07 ml to 5.35±0.1 ml. Administration of hydrochlorothiazide under the load of salts and water resulted in a higher excretion of sodium and potassium as compared to the effect of cornflower water extract. The highest prostaglandin levels were found in the plasma of the animals receiving hydrochlorothiazide. Under the load of salts and water, a 13% and 15% increase in the amount of prostaglandins observed in the animals given cornflower water extract compared to the control animals respectively (P<0.05). The greatest increase in the amount of kinins was found in the groups of animals that given hydrochlorothiazide under the load of salts and water (14% and 22%, respectively). Kinin levels did not differ significantly between the control group and the groups receiving cornflower water extract [131].

CONCLUSION

This paper reviewed the cardiac, cardioprotective, vascular effects of medicinal plants and plants affected blood pressure to open the door for their clinical uses as a result of efficacy and safety.
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