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CARDIOVASCULAR EFFECTS OF *CARTHAMUS TINCTORIUS* : A MINI-REVIEW

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ABSTRACT

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives. The recent studies showed that many plants possessed cardiovascular effects. This review was designed to cover the cardiac, cardioprotective, vascular, hypolipidemic, anti platelet aggregating and antioxidant effects of *Carthamus tinctorius*.

Key words: *Carthamus tinctorius*, Cardiac, Cardioprotective, Vascular, Hypolipidemic, Anti platelet aggregating, Antioxidant.

INTRODUCTION

Historically, *Carthamus tinctorius* has been restricted to the Middle East, part of Asia and Africa, but over time it has also been adapted to the semi-arid climatic areas[1, 2]**.** The chemical groups isolated from *Carthamus tinctorius* were included, oils, proteins, minerals, phenolics, flavonoids, alkaloids, lignans, carboxylic acids, steroids, polysaccharides, quinochalcone *C*-glycosides and quinone-containing chalcones [3-9]. Commercial safflower varieties contained 32 to 52 percent oil. The crop was divided into two categories based on oil quality: high linoleic acid varieties, and high oleic (monounsaturated fatty acid) acid varieties [1]. Many dyes [10] and serotonin derivatives were isolated from *Carthamus tinctorius* oil cake [5, 11-17]. The total phenolic contents were 126.0±2.4 (mg, gallic acid equivalent/g), and the total flavonoid contents were 62.2±1.9 (mg, quercetin equivalent/g). Phenolic compounds identified in *Carthamus tinctorius* seed extract were included (mg/g) hydroxybenzhydrazide derivative 18.2, amino-3,4-dimethylbenzoic acid 16.8, chlorogenic acid 2.4, syringic acid 0.2, p-coumaric acid 0.5, trans-Ferulic acid 3.0, gallocatechin 17.0, -(-)epigallocatechin 109.6, epigallocatechin gallate 1.1, quercetin dehydrate 2.2, kaempferol 0.8, rutin hydrate 3.7, luteolin 1.6, naringin 6.0 and trans-chalcone 2.1 [18, 19]. Quinochalcone compounds, saffloquinoside A, saffloquinoside B and quinochalcone C-glycosides were isolated from the florets of *Carthamus tinctorius* [20-21]. Many Erythro - alkane-6,8-diols compounds were isolated from the flowers of *Carthamus tinctoriu*, triterpenoid saponin [22] and linear polyacetylene glucosides [23] and lignan glycosides were also isolated from seeds of *Carthamus tinctorius* [24]. It was also rich nutritional composition plant [25-27]. The recent studies showed that many plants possessed cardiovascular effects [28-76]. This study was designed to cover the cardiac, cardioprotective, vascular, hypolipidemic, anti platelet aggregating and antioxidant effects of *Carthamus tinctorius***.**

Cardiac and cardioprotective effects

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 H_2O_2 exposure. Pretreatment with 100-400 microg/ml ECT prior to H_2O_2 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 H_2O_2-induced cardiomyocyte apoptosis, as detected by Annexin V and PI double labeling with flow cytometry.

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ECT pretreatment significantly inhibited H_2O_2-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 mediating the PI3K signaling pathway [77].

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 [78].

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 [79].

The protective effects of N-(p-Coumaroyl)serotonin (C) and N-feruroylserotonin (F) were investigated in perfused guinea-pig Langendorff hearts subjected to ischemia and reperfusion. Changes in cellular levels of high phosphorous energy, NO and Ca^{2+} 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-Ca^{2+} signals (TCa) and transient O_2 signals detected with a pO_2 electrode. At the final stage of ischemia, the intracellular concentration of Ca^{2+} 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 Ca^{2+} 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 [80].

The effect 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 IkappacB 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 [81].

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) [82].

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 (cTnI) (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) [83].

The protective effect of safflor 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 [84].

Vascular effects

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 [85].

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 [86].

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 tissure was measured by TUNEL method and caspase-3 concentration was measured by immune-histochemistry. 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 [87].

The vasodilatation effects of hydroxysafflor 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) [88]. 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 [89].

The therapeutic and preventive effects of Safflower Injection (Al) 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%, $P<0.05$) [90].

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 Ca^{2+} concentration that was induced by KCl or 5-hydroxytryptamine in cultured rat vascular smooth muscle cells (VSMCs). The effects of CS and FS were 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 Ca^{2+} 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 [91].

The effects of Safflower (Chinese Tradional Medicine) on the intestine ultrastructure characteristics during intestine ischemia/ reperfusion injury (I/RI) were 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 [92].

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 [93].

The effects of defatted safflower seed extract and its phenolic constituents, serotonin derivatives, on atherosclerosis were studied. Ethanol-ethyl acetate 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 $CuSO_4$-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 [94].

The modifying effect of hydroxysafflor 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 [95].

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 [96].

The effect of Safflower injection was evaluated on pulmonary hypertension in rat 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 [97].

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 [98].

Effect on platelet aggregation

The effects of The carthamins yellow (CY) was studied on a blood stasis model, which was obtained by placing rats in ice-cold water during the time interval between two injections of epinephrine. The results demonstrated that CY significantly decreased the whole blood viscosity, plasma viscosity, and erythrocyte aggregation index, which were increased in the blood stasis model. Hematocrit and platelet aggregation were reduced, while prothrombin time was delayed with increasing doses of CY [99].

Safflower yellow inhibited the PAF induced washed platelet aggregation and 5-HT release in a dose dependent manner. When the PAF was 2.0×10^{-9} mol/l, the inhibition rate of platelet aggregation was 26.2%, 41.3%, 58.1%, 81.2%, and the inhibition rate of 5-HT release was 3.7%, 11.9%, 29.9% and 54.4% after treatment with safflower yellow at 0.21, 0.42, 0.85 and 1.69 g/l, respectively. Accordingly, safflower yellow can inhibit the PAF induced platelet aggregation, 5-HT release by platelets and elevation of free calcium in platelets [100]. Intraperitoneal administration of 30 mg of an aqueous extract of the flowers to mice reduced platelet aggregation induced by adenosine diphosphate (ADP) by 65% in γ-irradiated animals [101].

Hypolipidemic effects

The effect of the extracts from safflower was investigated on cholesterol metabolism in high cholesterol fed rats. After treatment for 14 and 30 days, a significant reduction in total cholesterol and total cholesterol/HDL-cholesterol and a significant induction in HDL-cholesterol were observed in the hypercholesterolemic rats treated with the dichloromethane extract. Higher expression of SRBI and ABCA1 in the liver of the control group was observed after 4 weeks whereas no significant difference in the expression level of SRBI and ABCA1 was found in groups treated with extract after 2 and 4 weeks. The authors suggested that the expression of SRBI and ABCA1 mRNA may not be regulated by the crude extract of safflower, which may not in part explain the decrease in HDL-cholesterol and gene encoding enzymes of the cholesterol biosynthetic pathway [102].

The inhibitory effects of defatted safflower seed extract (SSE) and serotonin derivatives (N-p-coumaroyl serotonin and N-feruloyl serotonin, CS+FS), were evaluated on hypercholesterolemia and atherosclerosis, using Pulse wave velocity (PWV) in Kurosawa and Kusanagi-hypercholesterolemic rabbits. The atherosclerotic lesioned area in the aorta was significantly reduced in the SSE and CS+FS groups, without significant changes in serum cholesterol and triglyceride levels among the three groups after supplementation. Local PWV (LPWV) in the middle thoracic and distal abdominal aortas was significantly smaller in the SSE and CS+FS groups than in the control group. PWV in the entire aorta was also significantly lower in the SSE and CS+FS groups, compared with that in the control group. Pressure-strain elastic modulus, an index of wall distensibility, was significantly lower in the middle thoracic and middle abdominal aortas in the SSE and CS+FS groups than in the control group. Wall thickness was also significantly smaller in the middle thoracic aorta in the SSE and CS+FS groups compared with that in the control group [16].

Antioxidant effect

Antioxidative activities of serotonin derivatives isolated from safflower oil were measured by ferric thiocyanate method and DPPH method and the compounds showed storage antioxidative activity [14].

Carthamus red isolated from safflower (*Carthamus tinctorius*), was evaluated for antioxidant and hepatoprotective activity. An *in vivo* study against CCl_4-induced liver injury was conducted and compared with that of silymarin, a known hepatoprotective drug. Carthamus red did not show any toxicity and mortality up to 2000 mg/kg dose, and it showed strong antioxidant ability *in vitro*. In the *in vivo* study, carthamus red treatment lowered the serum levels of ALT, AST, ALP and total protein in liver damage rat models. Meanwhile, Nrf2, GSTα and NQO1 expressions were up-regulated at the protein level. Additionally, the activities of antioxidant enzymes and level of GSH were elevated by carthamus red, while the content of TBARS, which is an oxidative stress marker, was lessened. Histological examination showed that the condition of liver damage was mitigated [103].

Carthamus tinctorius L. seed extract (CSE) exhibited remarkable radical scavenging activities, FRAP (ferric reducing antioxidant power) and reducing power in a dose-dependent manner. Moreover, the oxygen radical absorbance capacity (ORAC) value of CSE (0.1 mg/ml) was 62.9 ± 4.7 μM TE (trolox equivalent)/g. During adipogenesis, CSE significantly inhibited fat accumulation in 3T3-L1 cells compared with control [18].

Antioxidative activities of serotonin derivatives isolated from safflower (*Carthamus tinctorius* L.) oil cake were measured by two methods. Five of serotonin derivatives were found to have relatively strong antioxidative activity [12].

Carthamus tinctorius flavonoids were evaluated against 2-deoxyribose degradation and rat liver microsomal lipid peroxidation induced by hydroxyl radicals generated via a Fenton-type reaction. Among the *Carthamus tinctorius* flavonoids, luteolin-acetyl-glucoside and quercetin-acetyl-glucoside showed potent antioxidative activities against 2-deoxyribose degradation and lipid peroxidation in rat liver microsomes. Luteolin, quercetin, and their corresponding glycosides also exhibited strong antioxidative activity, while acacetin glucuronide and apigenin-6,8-di-C-glucoside were relatively less active [19].

The *in vitro* antioxidant activities of extracts of *C. tinctorius* (ECT) and the main antioxidant components of ECT were determined by HPLC. The results show that flavonoids were the main components of ECT and were active in scavenging OH^{1-} and O^{2-} and DPPH, in a dose-dependent manner [104].

Free radical scavenging activity of the extracts of petals (bud, early stage, full blooming and ending stage), leaf, stem, root and seeds of Mogami-benibana (safflower, *Carthamus tinctorius* Linne) was evaluated. The scavenging activities of the extract of safflower petals with various colors showed antioxidant activity. There was also a relationship between DPPH radical scavenging activity and carthamin content in the petal extracts of safflower [105].

In studying the antioxidant effects of water extract of *Carthamus tinctorius* on ox-LDL induced injury in rat cardiac microvascular endothelial cell and detecting oxygen derived free radicals (OFR) to explore the antioxidant mechanisms. It appeared that water extract of *C. tinctorius* increased the rCMEC survival rate, reduced LDH, MDA and XOD levels, and improved SOD, GSH-Px and NOS activity, while in the cell suspension ROS signal decreased significantly [106].

The potential protective effects of *C. tinctorius* flower extract (CFE) against reactive oxygen species (ROS) induced osteoblast dysfunction were investigated using osteoblastic MC3T3-E1 cells. The osteoblast function was assessed by measuring alkaline phosphatase activity, collagen content, calcium deposition, and RANKL production, and the oxidative status was assessed by measuring intracellular lipid peroxidation, and protein oxidation in osteoblastic MC3T3-E1 cells. A significant reduction in the alkaline phosphatase activity, collagen, and calcium deposition and an increase in the production of receptor activator of nuclear factor-kB ligand (RANKL) were observed after 0.3 mM H_2O_2 addition. The H_2O_2-induced alterations were prevented by pre-incubating the osteoblasts with 2-10 microg/ml CFE for 48 h. When the oxidative stress was induced by H_2O_2, the increased production of protein carbonyl and malondialdehyde was also reduced at the same CFE concentration [107].

The protective effect of safflor yellow B (SYB) was investigated on the acute oxidative injury induced by H_2O_2 in PC12 cells. The results showed that exposure of the cells to H_2O_2 significantly decreased the cell viability, SOD and GSH-Px activities and Bcl-2 expression, and increased LDH release, superoxide anion and MDA generations, caspase 3 activity and Bax expressions. Pretreatment of the cells with SYB was able to remarkably antagonize the H_2O_2-induced changes in dose-dependent way. SYB is able to protect PC12 cells from H_2O_2-induced injury and apoptosis via antioxidant and anti-apoptotic mechanisms [108].

CONCLUSION

This review cover the cardiac, cardioprotective, vascular, hypolipidemic, anti platelet aggregating and antioxidant effects of *Carthamus tinctorius* to be used in medical practice as a result of efficacy and safety.

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