GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Hypotensive and vascular activities of medicinal plants

Ali Esmail Al-Snafi *

Department of Pharmacology, College of Medicine, University of Thi qar, Iraq.

GSC Biological and Pharmaceutical Sciences, 2022, 19(03), 044–063

Publication history: Received on 28 April 2022; revised on 31 May 2022; accepted on 02 June 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.19.3.0214

Abstract

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals preparations. The previous studied showed that many medicinal plants possessed hypotensive effects and affected vascular activity either by direct effect on vascular smooth muscles or indirectly by affecting endothelium vasoactive substances. The current review was designed to highlight the medicinal plants with hypotensive and vascular effects as promising future therapies because of efficacy and safety.

Keywords: Hypertension; Hypotensive; Vasoactive; Vascular; Medicinal plants

1. Introduction

Hypertension is the most common chronic health problem and represents one of the high risk factors for myocardial infarction, arteriosclerosis, stroke, and end-stage renal disease. On the other hand, atherosclerotic ischemic heart disease is one of the largest leading cause of general mortality. Vascular endothelium releases many vasoactive substances, which regulated and maintained the overall cardiovascular homeostasis. The previous studied showed that many medicinal plants possessed hypotensive effects and affected vascular activity either by direct effect on vascular smooth muscles or indirectly by affecting endothelium vasoactive substances[1-3]. The current review highlighted the medicinal plants with hypotensive and vascular effects as promising future therapies because of efficacy and safety.

1.1. *Adonis vernalis*

Tincture of *Adonis vernalis* was evaluated as hypotensive therapy. The dog blood pressure response was varied with dose, low doses showed rise in blood pressure whereas larger doses showed fall in blood pressure [4].

1.2. *Agrimonia eupatoria*

A hypotensive effect in anaesthetized cats has been documented for an agrimony extracts given by intravenous injection; blood pressure was lowered by more than 40% [6].

1.3. *Allium sativum*

Experimental and clinical studies showed that garlic produced hypotensive effects. Garlic induced significant reduction in systolic and diastolic blood pressure [7-12].

1.4. *Althaea rosea*

The alcoholic extract showed a transient hypotensive effect on anesthetic cats [13].

*Corresponding author: Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, University of Thi qar, Iraq.

1.5. *Ammi visnaga*

Visnadine 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 [14-16].

A chloroform, and methanol extract (1mg/ml) of the fruits inhibited the potassium chloride induced contractions of the rabbit guinea-pig aorta in vitro [17-18].

Visnadin, 60.0 μg/ml or 120.0 μg/ml, increased coronary blood flow in isolated guinea-pig hearts by 46% and 57% respectively [19-20].

Visnagin inhibited the contractile responses induced in rat aortic rings by: (a) KCl or increases of extracellullar Ca^{2+} in KCl depolarized aortic rings, its effects being more potent against low (20 mM) than high (80 mM) KCl-induced contractions, (b) noradrenaline in Ca^{2+}-containing solution and less effectively those in Ca^{2+}-free solution and (c) phorbol 12-myristate 13-acetate (PMA) in a Ca^{2+}-containing and with a lower potency in Ca^{2+}-free medium. The relaxation induced by visnagin in aorta pre-contracted with noradrenaline was not affected by endothelium removal. Additionally, visnagin inhibited the spontaneous myogenic contractions of portal veins. The results showed that visnagin inhibited vascular smooth muscle contractility by acting at multiple sites [21]. 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 heart rate [22].

1.6. *Anethum graveolens*

Intravenous administration of 5–10 mg/kg body weight of 5% seed oil in saline to cats caused hypotension and increased respiration volume [23-25].

1.7. *Apium graveolens*

The effects of aqueous and ethanol extracts (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) [26-27].

1.8. *Arachis hypogaea*

Bioactive peptides with antihypertensive effects against angiotensin converting enzyme were isolated from peanut [28-29].

1.9. *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 angiotensine 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 [30-32].

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 [33-34].

1.10. *Bryophyllum calycinum*

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 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 [36-38].

1.11. *Caesalpinia crista*

The administration of aqueous leaf extract induced a progressive decrease of blood pressure. The hypotensive action of the extract was dose-dependent and reversible. 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 [39-40].

1.12. *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). The *in vitro* vasomotor effects of aqueous extract of roots, leaves, stems, flowers, fruits and kernels were evaluated on the rings of thoracic aorta and windpipe of rat. The addition of extracts with different concentrations during the stage of contraction led by the phenylephrin for the thoracic arteries showed a light vasodilatation. Furthermore 30 min incubation with extracts at different concentrations showed a significant vasodilator effect for fruits and kernels, and vasoconstrictor effect for leaves [41-43].

1.13. *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 [44].

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) [45].

Intravenous injection of the hydroxysafflor yellow A (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 [46-47].

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) [47-48].

1.14. *Chamaemelum nobile*

Single oral administration of *C. nobile* aqueous extract (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 produced a significant increase in urinary output and electrolytes excretion ($p < 0.01$) from the day 8 to the end of treatment. The in vitro vaso relaxant 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 10-5) M ($p < 0.001$) [49-50].

1.15. *Cicer arietinum*

Treatment of legumin of *Cicer arietinum* with alcalase yielded a hydrolysate that inhibited the angiotensin I converting enzyme with an IC_{50} of 0.18 mg/ml. Fractionation of this hydrolysate by reverse phase chromatography afforded six inhibitory peptides with IC_{50} values ranging from 0.011 to 0.021 mg/ml. All these peptides contain the amino acid

methionine and are also rich in other hydrophobic amino acids. Hydrolysates of chickpea legumin obtained by treatment with alcalase are a good source of peptides with angiotensin-1converting enzyme inhibitory activity [51-52].

1.16. *Cichorium intybus*

The vaso relaxant activities of chicoric acid from *Cichorium intybus* along with caffeic acid were studied in isolated rat aorta strips. Chicoric acid, a diester composed of (S, S)-tartaric acid and caffeic acid, showed slow relaxation activity against norepinephrine (NE)-induced contraction of rat aorta with/without endothelium. These compound did not affect contraction induced by a high concentration of potassium (60 mM K+), while it inhibited NE-induced vaso contraction in the presence of nicardipine. The results revealed that the inhibition of NE-induced vaso contraction is due to a decrease in calcium influx from the extracellular space, which enhanced by NE [53-54].

1.17. *Cistanche tubulosa*

The vasorelaxant activity of echinacoside, a phenylethanoid glycoside isolated from *Cistanche tubulosa*, and its possible underlying mechanism on isolated rat thoracic aortic rings pre-contracted with phenylephrine (PE, 1 microM) and KCl (60 mM) was investigated. Echinacoside (30-300 microM) exhibited an acute relaxation in endothelium-intact rings in a concentration-dependent manner, while this relaxation was significantly inhibited in endothelium-denuded condition and in the presence of the endothelial nitric oxide synthase (eNOS) inhibitor, N (W)-nitro-L-arginine methyl ester (L-NNA, 100 microM), an unselective soluble guanylate cyclase blocker, methylene blue (10 microM) and the selective sGC inhibitor 1 H-[1, 2, 4] oxadiazolo[4,3- A]quinoxalin-1-one (ODQ, 1 microM); in addition, atropine (1 microM), a selective muscarinic receptor antagonist, partially affected the relaxation. However, the cyclooxygenase inhibitor indomethacin (5 microM) had no influence on the relaxant action. Echinacoside enhanced the cyclic guanosine monophosphate (cGMP) production in aortic rings contracted with PE. The authors concluded that echinacoside mediates the endothelium-dependent vasodilator action in rat thoracic aortic rings through nitric oxide (NO)-cGMP pathway. The methanolic extract from the dried stems of *Cistanche tubulosa* showed inhibitory effect on contractions induced by noradrenaline in isolated rat aortic strips. From the extract, new phenylethanoid oligoglycoside constituents, kankanosides F and G, and an acylated oligosugar, kankanose, were isolated together with 14 known compounds. Kankanoside F, kankanose, echinacoside, acteoside, and cistanoside F, showed vaso relaxant activity [55-56].

1.18. *Citrus species*

The effect of drinking the juice of two different citrus fruits on vascular neointima formation was studied using a cuff-induced vascular injury mouse model. Male C57BL6 mice were divided into five groups as follows: 1) Control (water) (C), 2) 10% citrus unshiu (CU) juice (CU10), 3) 40% CU juice (CU40), 4) 10% citrus iyo (CI) juice (CI10), and 5) 40% CI juice (CI40). After drinking them for 2 weeks from 8 weeks of age, cuff injury was induced by polyethylene cuff placement around the femoral artery. Neointima formation was significantly attenuated in CU40, CI10 and CI40 compared with C. However, no remarkable preventive effect was observed in CU10. The increases in levels of various inflammatory markers including cytokines such as monocyte chemotactic protein-1, interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α in response to vascular injury did not differ significantly between C, CU10 and CI10. The increases in cell proliferation and superoxide anion production were markedly attenuated in CI10, but not in CU10 compared with C. The increase in phosphorylated ERK expression was markedly attenuated both in CU10 and CI10 without significant difference between CU10 and CI10. Accumulation of immune cells did not differ between CU10 and CI10. The results indicate that drinking citrus fruit juice attenuates vascular remodeling partly via a reduction of oxidative stress [57].

The cardiovascular effects of *Citrus aurantifolia* fruit were studied experimentally. The anti-hypertensive effect was tested on three experimental hypertensive models including cadmium induced hypertensive model, glucose induced hypertensive model, Egg feed diet induced hypertensive model, and normotensive model. The systolic pressure, diastolic pressure, mean blood pressure and heart rate of Spargue Daweley rats were measured by tail cuff method from the tail of rats using non-invasive blood pressure instrument and body weights were also measured. Three different doses were used for screening 0.25, 05, and 0.75g/kg, orally given and there effects on normotensive rats were observed at 2hr, 4hr and 6hr intervals. The dose of 0.75g/kg was selected because it significantly reduced the mean blood pressure, systolic blood pressure, diastolic blood pressure, and heart rate. The methanol extract of *Citrus aurantifolia*, administered at the dose of 0.75mg orally, significantly ($p<0.01$) reduced systolic blood pressure, mean blood pressure, diastolic blood pressure, heart rate and body weight of Spargue Dawely rats in both normotensive and hypertensive experimental models when compared to control groups [58].

The effect of an aqueous extract of *Citrus aurantifolia* on arterial blood pressure and on isolated heart and aorta activities was evaluated experimentally. Rabbits were used for the study on the arterial blood pressure using a Ludwig

manometer. Albino Wistar rats were used for the isolated heart and aorta activities using isolated organ bath systems. Aqueous extract of *Citrus aurantifolia* (4mg/kg-16mg/kg bw) produced a dose-dependent and significant decrease in rabbit blood pressure ($p<0.05$). This hypotension was not prevented by atropine (2 mg/kg bw, $p>0.05$). Aqueous extract (4mg/kg-16mg/kg bw) was dose-dependently reduced hypertension evoked by adrenalin (30 µg/kg bw). The extract also induced both negative inotropic and chronotropic effects on the heart contractile activity. The extract induced a dose dependent relaxation of contractions produced by adrenalin or by KCl. Aqueous extract of *Citrus aurantifolia* evoked vaso relaxant effects were totally abolished by removal of the endothelium layer or by a pretreatment with L-NAME [59].

The antihypertensive effect of *C. medica limetta* leaves was investigated against the acute response of blood pressure to angiotensin II administration The results showed that different concentrations of the aqueous extract prevented the raise of systolic blood pressure ($p\leq0.001$ vs. vehicle), diastolic blood pressure ($p \leq 0.0002$ vs. vehicle) and mean blood pressure ($p \leq 0.0000$ vs. vehicle); with a dose dependent effect for diastolic pressures at 125–500 mg/kg dosages. The 500 and 1000 mg/kg doses inhibited the action of Ang II in similar extent to telmisartan. Toxic signs or deaths were not observed in mice treated with a dose of 2000 mg/kg [60].

Four-week consumption of orange juice in healthy middle-aged, normal-weight men reduced diastolic blood pressure (DBP). However, the effects of four-week intake of natural and commercial orange (*Citrus sinensis*) juice (CSJ) on blood pressure was evaluated in healthy volunteers. 22 healthy subjects were included and randomly divided into two groups. Group A consumed commercial CSJ during the first four-week period. After a two-week washout period, they consumed natural CSJ for another four weeks. The procedure was reversed in group B. The participants were asked to drink 500 ml/day of either natural or commercial CSJ twice a day with breakfast and dinner. After drinking commercial CSJ, diastolic and systolic blood pressure were significantly decreased (5.13%; $P = 0.03$ and -5.91%; $P = 0.003$, respectively). However, consumption of natural CSJ did not have significant effects on either diastolic or systolic blood pressure. Higher flavonoid, pectin, and essential oils content of concentrated products compared to natural juice might have been responsible for this effect [61].

An attempt was made to isolate hypotensive substances from a hot water extract of *Citrus unshiu*. Six flavonoid glycosides were isolated by repeated chromatography and gel filtration after extraction with butanol and treatment with lead subacetate. Each component was intravenously injected into SHR-SP rats (1 mg/100g body weight), 3, 6-di-C-glucosylapigenin and rutin were found to lower their blood pressure [62-63].

1.19. *Cordia myxa*

Mucilage from both ripe and unripe *Cordia obliqua* (RCo and URCo) decreased rabbit blood pressure and stimulated the respiratory rate. URCo was 12.37-fold more potent as a hypotensive agent than RCo. Investigation of the mode of action revealed that the hypotensive effect was more likely due to activation of parasympathetic ganglia and dilatation of peripheral blood vessels [64-65].

1.20. *Coriandrum sativum*

Coriander crude extract (1-30 mg/ml) caused fall in arterial blood pressure of anesthetized animals which partially blocked by atropine. Coriander crude extract produced vasodilatation against phenylephrine and K+ (80 mM)-induced contractions in rabbit aorta and caused cardio-depressant effect in guinea-pig atria. Bioassay-directed fractionation revealed the separation of spasmogenic and spasmolytic components in the aqueous and organic fractions respectively. Furthermore, Coriander crude extract produced diuresis in rats at 1-10mg/kg [66-67].

The water extract of coriander seed had hypotensive effects in rats. Aqueous extracts of coriander seeds inhibited the electrically- evoked contractions of spiral strips and tubular segments of isolated central ear artery of rabbit [68-69].

1.21. *Crocus sativus*

The effect of *Crocus sativus* on Ca^{2+} influx in isolated rat aortas was investigated by using ^{45}Ca as a radioactive tracer. Ca^{2+} uptake in isolated rat aorta rings in normal physiological status was not markedly altered by these drugs, whereas the Ca^{2+} influxes induced by norepinephrine of 1.2 mmol/l and KCl of 100 mmol/l were significantly inhibited by crocus in a concentration-dependent manner. The results showed that extracellular Ca^{2+} influx through receptor-operated Ca^{2+}channels and potential dependent Ca^{2+}channels can be blocked by crocus [70].

The effects of *Crocus sativus* petals' extract on blood pressure was evaluated on anaesthetized rats. Aqueous and ethanol extracts of *Crocus sativus* petals reduced the blood pressure in a dose-dependent manner. Administration of 50mg/100

g of aqueous extract changed the blood pressure from 133.5±3.9 to 117±2.1 (mmHg). The effects of saffron (*Crocus sativus*) stigma aqueous extract and two active constituents, crocin and safranal, were investigated on blood pressure of normotensive and desoxycorticosterone acetate-induced hypertensive rats. Three doses of crocin (50, 100 and 200 mg/kg), safranal (0.25, 0.5 and 1 mg/kg) and the aqueous extract (2.5, 5 and 10 mg/kg) were administered intravenously in different groups of normotensive and hypertensive animals and their effects on mean arterial blood pressure (MABP) and heart rate (HR) were evaluated. The aqueous extract of saffron stigma, safranal and crocin reduced the MABP in normotensive and hypertensive anaesthetized rats in a dose-dependent manner. Administrations of 10 mg/kg of aqueous extract, 1 mg/kg of safranal and 200 mg/kg of crocin caused 60 ± 8.7, 50 ±5.2 and 51 ± 3.8 mmHg reductions in MABP, respectively. Accordingly, the aqueous extract of saffron stigma had hypotensive properties which appear to be attributable, in part, to the actions of two major constitutes of this plant, crocin and safranal, and safranal was more important than crocin for lowering the blood pressure of rats [71].

The effects of saffron (*Crocus sativus*) stigma aqueous extract was studied on blood pressure of normotensive and desoxycorticosterone acetate (DOCA)-salt induced hypertensive rats. Five weeks administration of three doses saffron aqueous extract (10, 20 and 40 mg/Kg/day) and spironolactone (50 mg/Kg/day) in different groups of normotensive and hypertensive rats (at the end of 4 weeks treatment by DOCA-salt) showed that chronic administration of saffron aqueous extract reduced the MSBP in DOCA salt treated rats in a dose dependent manner. It did not decrease the MSBP in normotensive rats. The data also showed that the antihypertensive effects of saffron did not persist [72].

The vasomodulatory effect of crocetin was analyzed in hypertension. Myographical experiments were performed to compare the relaxation induced by acetylcholine (ACH) on aortic rings from normotensive (Wistar) and hypertensive (SHR) rats, incubated with or without crocetin or saffron extract and L-NAME or indomethacin. Extracts were also assayed in deendothelialized rings. Crocetin enhanced the ACH relaxations in aorta from hypertensive (strongly) and normotensive rats (weakly). Crocetin plus L-NAME abolished the relaxant response in SHR but not in Wistar aorta. Crocetin plus indomethacin did not modify the indomethacin response in either SHR or Wistar aorta. Crocetin in rubbed segments did not modify the ACH responses. In contrast, saffron increased this response in rubbed segments from SHR but not Wistar rats. Accordingly, crocetin exerts healthy vasomodulatory effects in hypertension, strongly improving endothelium-dependent ACH relaxations via endothelial nitric oxide but not the cyclooxygenase pathway [73-74].

1.22. *Cuminum cyminum*

The anti-hypertensive potential of standardized aqueous extract of *Cuminum cyminum* seeds and its role in arterial endothelial nitric oxide synthase expression, inflammation, and oxidative stress were evaluated in renal hypertensive rats. Renal hypertension was induced by the two-kidney one-clip (2K/1C) method in rats. Systolic blood pressure (SBP), plasma nitrate/nitrite, carotid–eNOS, renal–TNF-α, IL-6, Bax, Bcl-2, thioredoxin 1 (TRX1), and thioredoxin reductase 1 (TRXR1) mRNA expressions were studied to demonstrate the anti-hypertensive action of *Cuminum cyminum*. *Cuminum cyminum* seed was administered orally (200 mg/kg bw) for a period of 9 weeks, it improved plasma nitric oxide and decreased the systolic blood pressure in hypertensive rats. It also up-regulated the gene expression of eNOS, Bcl-2, TRX1, and TRXR1; and down-regulated Bax, TNF-α, and IL-6. The data revealed that *Cuminum cyminum* seeds augment endothelial functions and ameliorate inflammatory and oxidative stress in hypertensive rats [75-76].

1.23. *Cydonia oblonga*

The effect of ethanol leaf extracts of *Cydonia oblonga* Mill. (COM) was studied on hypertension and on biomarkers associated with blood pressure control, such as angiotensin-II (AII), plasma renin activity (PRA), apelin-12 (A), endothelin (ET) and nitric oxide (NO), compared to captopril. Two-kidney one-clip (2K1C) Goldblatt model rats were divided randomly into six groups: sham, model, captopril 25 mg/kg, COM leaf extract 80, 160 and 320 mg/kg. Drugs were administered orally daily for eight weeks. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before treatment and every 2 weeks. Blood and kidney samples were collected after the last treatment to measure AII, PRA, A, ET and NO. Renal hypertensive rats (RHR) had increased blood pressure, AII, A, PRA, ET and decreased NO. Treatment with captopril reduced blood pressure, AII, A, PRA, and ET, though not quite to normal values. COM leaf extracts significantly and dose-dependently reduced blood pressure, AII, A, RA and ET, whereas NO was increased. The effects of COM extracts on blood pressure and biomarkers were dose-dependent and at the highest dose, it produced effects similar to those of captopril [77].

The effects of *Cydonia oblonga*. (COM) fruit and leaf extracts on blood pressure and rheology were studied in renal hypertensive rats (RHR). Daily doses of 80 and 160mg/kg aqueous or ethanol extracts of COM fruit or leaves, or 25mg/kg captopril were given orally once daily for 8 weeks. Blood pressure was measured before treatment and every 2 weeks thereafter. Blood rheology was tested after 8 weeks. Model rats had higher blood pressure than sham, 8 weeks after the procedure (systolic blood pressure 193±7 vs. 138±8mmHg, $p<0.05$). Those treated with captopril had

decreased blood pressure within 2 weeks but that did not return to the level found in the sham group at 8 weeks (167±7, $p<0.05$ vs. model). With the COM extracts, the effect on blood pressure was notable after 4 weeks. At 8 weeks blood pressure was similar with captopril and with 160mg ethanol leaf extract (166±4, $p<0.05$ vs. model), it was the most effective of the extracts. Model rats had higher blood viscosity and lower erythrocyte deformability than sham. Captopril had little effect on blood rheology; whereas COM extracts reduced whole blood viscosity and improved erythrocyte deformability to levels approaching those found in sham [78-79].

1.24. *Daucus carota*

Ethanolic extract of *Daucus carota*at the dose of 10–100 mg/kg caused a dose-dependent fall in systolic and diastolic arterial blood pressure in normotensive anesthetized rats. These effects were not blocked by atropine (1 mg/kg). Pretreatment with *Daucus carota*did not alter the pressor response to norepinephrine indicating that, cardiovascular effects of *Daucus carota* were independent of cholinergic or adrenergic receptors involvement. In spontaneously beating guinea-pig paired atria, *Daucus carota* induced a concentration-dependent (0.3-5 mg/ml) decrease in force and rate of atrial contractions. In rabbit thoracic aorta, *Daucus carota* caused inhibition of K^+-induced contractions at similar concentrations [80-81].

Fractionation of aerial parts of *Daucus carota* resulted in the isolation of two cumarin glycosides coded as DC-2 and DC-3. Intravenous administration (1-10mg/kg) of these compounds caused a dose-dependent fall in arterial blood pressure in normotensive anaesthetized rats, Both compounds caused a dose-dependent (10-200 pg/ml) inhibitory effect on spontaneously beating guinea pig atria as well as on the Kt-induced contractions of rabbit aorta at similar concentrations *in vitro*. The results indicated that DC-2 and DC-3 acting through blockade of calcium channels, the effect which may be responsible for the blood pressure lowering effect of the compounds observed in the *in vivo* studies [81-82].

1.25. *Foeniculum vulgare*

The hypotensive effects of the water extract of *Foeniculum vulgare* were investigated in spontaneously hypertensive rats (SHR) and in normotensive Wistar-Kyoto rats (WKY). Oral administration of *Foeniculum vulgare* extract lowered the systolic blood pressure of SHR but not of WKY. In SHR, *Foeniculum vulgare* treatment increased water, sodium and potassium excretion. *Ex vivo* as well as *in vitro*. *Foeniculum vulgare* extract inhibited the contractile responses of rat aorta to noradrenaline which blocked by N-nitro-L-arginine [83-84].

1.26. *Fritillaria imperialis*

In anesthetized dogs, the alkaloidal fraction isolated from the corms of *Fritillaria imperialis* showed an appreciable fall in blood pressure due to cardiac depression and peripheral vasodilatation. Hypotensive effect is also observed in experimental hypertension. On frog's heart the alkaloidal fraction exhibited cardiotonic effect. The alkaloidal fraction also exhibited anti-arrhythmic activity resembling that of quinidlne and spasmolytic activity similar to that of papaverine [85-86].

1.27. *Geum urbanum*

A 20% aqueous decoction of avens, administered by intravenous injection, has been reported to produce a reduction in blood pressure in cats [87-88].

1.28. *Haplophyllum tuberculatum*

The aqueous extract of *H. tuberculatum* significantly decreased the contractility and the heart rate but did not affect the flow rate of isolated perfused rabbit heart. The effect of the aqueous extract was not blocked by atropine. Aqueous extract caused fall in the blood pressure when administered to anaesthetized cats, muscarinic antagonist blocked the fall in blood pressure in cats. The extract also stimulated rabbit aortic strip, rat vas deferens, and rat anococcygeus muscles. These adrenergic effects were largely reduced by phentolamine [89-90].

1.29. *Hibiscus rosa-sinensis*

The effect of the aqueous leaves extract (200 mg/kg) of *Hibiscus rosa-sinensis* was investigated on the renal function of hypertensive rats. Although *H. rosa-sinensis* leave extract reduced blood pressure, but it induced significant ($p < 0.05$) increase in the Na^+ level of normotensive rats, thus it may interfere with the normal function of the kidney and hence produce increased salt retention [91-92].

1.30. *Hibiscus sabdariffa*

Hibiscus sabdariffa crude extract induced mainly endothelium-dependent relaxant effects on isolated thoracic aorta of male Wistar rats. The endothelium-dependent relaxations result from NOS activation [93-94].

Roselle calyx infusion was found to lower significantly ($p<0.05$) both systolic and diastolic pressure in spontaneously hypertensive and normotensive Wistar-Kyoto rats at tested doses of 500 and 1000 mg/ kg bw. The reduction in blood pressure in both groups was positively correlated with weight [95].

The aqueous extract of *Hibiscus sabdariffa* calyx attenuated the development of salt-induced hypertension in Sprague-Dawley rats treated for 12 weeks [96-97]

The aqueous extract of petals of *Hibiscus sabdariffa* (HS) also attenuated the established stages of 2-Kidney, 1-Clip renovascular hypertension in Sprague-Dawley rats [98].

Hibiscus sabdariffa ingestion in rat (10%, 15% and 20% of the water extract in drinking water for 10 consecutive weeks) significantly reduced Systolic (SBP), diastolic (DBP) and left ventricles (LV) mass in a dose-dependent fashion but did not affect the heart rate. It significantly increased surface area and length density of myocardial capillaries by 59%, 65% and 86%, and length density by 57%, 77% and 57%, respectively [99].

The anti-hypertensive activity of aqueous calyx extract of *Hibiscus sabdariffa* was investigated on salt induced hypertensive albino rats for 28 days. The extract treated groups showed a significant ($P < 0.01$) reduction in diastolic and systolic blood pressure when compared to the normotensive and hypertensive rats. There was no significant difference ($P > 0.05$) between the drug treated and the extract treated groups during this treatment [100].

Intravenous injection of aqueous extract of *Hibiscus sabdariffa* calyces to anaesthetized cats lowered the blood pressure in a dose-response manner. The inhibitory effects were resistant to a number of standard receptor blockers but the hypotensive influence was partially blocked by atropine [101].

A controlled and randomized clinical trial was carried out to compare the antihypertensive effectiveness and tolerability of a standardized extract from *Hibiscus sabdariffa* with captopril. Patients with diagnosed hypertension and without antihypertensive treatment for at least 1 month were included, they were received either an infusion prepared with 10 g of dry calyx from *Hibiscus sabdariffa* (9.6 mg anthocyanins content), daily before breakfast, or captopril 25 mg twice a day, for 4 weeks. The results showed that *Hibiscus sabdariffa* was able to decrease the systolic blood pressure (BP) from 139.05 to 123.73mm Hg ($p < 0.03$) and the diastolic BP from 90.81 to 79.52mm Hg ($p < 0.06$). At the end of the study, there were no significant differences between the BP detected in both treatment groups ($p > 0.25$). The rates of therapeutic effectiveness were 0.7895 and 0.8438 with *Hibiscus sabdariffa* and captopril, respectively ($p > 0.560$), whilst the tolerability was 100% for both treatments [102].

The daily consumption of extract of Hibiscus sepals significantly decreases systolic blood pressure (SBP) and diastolic blood pressure (DBP) in adults with pre to moderate essential hypertension and type 2 diabetes. The results revealed that the effectiveness of extract was equivalent to captropril, but less effective than lisinopril [103].

A randomized, double-blind, placebo-controlled clinical trial was conducted to determine the antihypertensive effects of *Hibiscus sabdariffa* tea consumption on 65 pre- and mildly hypertensive adults with no blood pressure-lowering medications. They used either three 240-ml servings/day of brewed hibiscus tea or placebo beverage for 6 wk. At 6 wk, hibiscus tea lowered systolic BP (SBP) compared with placebo. Diastolic BP was also lower, although this change did not differ from placebo. The change in mean arterial pressure was of borderline significance compared with placebo. Participants with higher SBP at baseline showed a greater response to hibiscus treatment [104].

Polyphenols from *Hibiscus sabdariffa* calices were administered to patients with metabolic syndrome (125 mg/kg/day for 4 wk) and spontaneously hypertensive rats (125 or 60 mg/kg in a single dose or daily for 1 wk). *Hibiscus sabdariffa* extract improved metabolism, displayed potent anti-inflammatory and antioxidant activities, and significantly reduced blood pressure in both humans and rats [105].

Clinical trials confirmed the antihypertensive effect using watery infusions. The results showed that the treatment decreased blood pressure (BP) from 146.48/97.77 to 129.89/85.96 mmHg, reaching an absolute reduction of 17.14/11.97 mmHg (11.58/12.21%, $p < 0.05$). The treatment showed therapeutic effectiveness of 65.12 % as well as

tolerability and safety of 100 %. BP reductions and therapeutic effectiveness were lower than those obtained with lisinopril ($p < 0.05$) [106].

The antihypertensive activity of roselle could be mediated by many mechanisms included inhibition of angiotensin-converting enzyme activity and subsequent renin-angiotensin-aldosterone system, (especially anthocyanins delphinidin-3-O-sambubioside,cyanidin-3-O-sambubioside and related flavonoid glycosides), enhancement of vascular activity by Na+ -K+ -ATPase and Ca^{2+}-Mg^{2+}-ATPase, enhancement of NO production, as endothelium derived relaxing factor (EDRF), attenuation of the discharge of the sympathetic nervous system and diuretic effects [105-115].

1.31. *Hyoscyamus niger*

Hyoscyamus niger crude extract (Hn.Cr) caused a dose-dependent (10-100 mg/kg) fall in the arterial blood pressure (BP) of rats under anesthesia. In guinea-pig atria, Hn.Cr exhibited a cardio-depressant effect on the rate and force of spontaneous atrial contractions. In isolated rabbit aorta, Hn.Cr (0.01-1.0 mg/ml) relaxed the phenylephrine (PE, 1 microM) and K^+ (80 mM)-induced contractions and suppressed PE (1 microM) control peaks obtained in Ca^{2+}-free medium similar to that caused by verapamil. The vasodilator effect of Hn.Cr was endothelium-independent as it was not opposed by N (omega)-nitro-L-arginine methyl ester in endothelium-intact rat aortic preparations and also occurred at a similar concentration in endothelium-denuded tissues [116-117].

1.32. *Hypericum triquetrifolium*

The vasorelaxant effect of the total extract of *Hypericum triquetrifolium* was investigated on rat isolated aortic rings. Contractions with phenylephrine and KC1 were compared after the tissues were incubated with different concentrations of *Hypericum triquetrifolium* extract. In addition, the inhibitory effect of *Hypericum triquetrifolium* extract (10^5-10^3 g/ml) on the sustained contractions of aorta with phenylephrine and KG was also investigated. The maximal inhibition obtained by the extract for the phenylephrine contractions was 93.95 ±5.23%, while the maximal inhibition was found as 85.78 ± 4.87 % for KC1 contractions. However, *Hypericum triquetrifolium* extract inhibited both phenylephrine and KC1 induced contractions in a concentration-dependent manner [118-119].

1.33. *Jasminum sambac*

The vasodilatation effect of the 95% ethanolic extract of *Jasminum sambac* flowers on isolated aortic rats was investigated. Compared with the control group, the Jasmine flowers extract in 0.05% DMSO reduced the tonus of isolated endothelium thoracic aortic rings pre-constricted with phenylephrine (10^{-6}µ M), dose-dependently. However, this effect was disappeared after the pre-incubation of the rings with atropine (10^{-6}µM) or with N^{ω}-nitro-L-arginine (10^{-4}µ M) [120-121].

1.34. *Juglans regia*

The walnut diet improved endothelium-dependent vasodilation and reduced levels of vascular cell adhesion molecule-1 ($P<0.05$). The walnut diet significantly reduced total cholesterol (-4.4±7.4%) and LDL cholesterol (-6.4±10.0%) ($P<0.05$) [122].

The effect of methanol extract of walnut (*Juglans regia* kernel extract 100 and 200 mg/ kg/day, orally) on dexamethasone-induced hypertension was studied in rats. Dexamethasone increased the diastolic BP and MDA/GPX ratio in comparison with control group (128 ± 7 vs. 105 ± 3 mmHg, $p < 0.05$ and 0.2 ± 0.046 vs. 0.08 ± 0.02, $p < 0.05$). Combination of dexamethasone and walnut (200 mg/kg) prevented the dexamethasone-induced diastolic hypertension (109 ± 3 vs. 128 ± 7 mmHg; $p < 0.05$), increased the GPX level (14.8 ± 1.46 vs. 5.1 ± 0.64 unit/mg, $p < 0.05$), reduced the MDA/GPX ratio (0.16 ± 0.015 vs. 0.2 ± 0.046) and improved serum NO level [123].

The potential anti-hypertensive effects of walnut was investigated clinically on130 hypertensive subjects. The result showed that *Juglans nigra* normalizes high blood pressure, high cholesterol and serum electrolytes if short term meal of walnut is taken. Walnut meal has no effect on haemoglobin concentration, white blood cell count, packed cell volume and platelet counts compared with their corresponding controls [124].

The effect of walnut methanolic extract and ellagic acid, one of its major polyphenolic components was studied on the expression of vascular cell adhesion molecule (VCAM)-1 and intracellular adhesion molecule (ICAM)-1 in human aortic endothelial cells. After incubating the cells with TNF-alpha (1 ng/ml) in the absence and in the presence of walnut extract (10-200 microg/ml) or ellagic acid (10- 7-10- 5 m), the VCAM-1 and ICAM-1 expression was quantified by cell-ELISA. Walnut extract and ellagic acid decreased significantly the TNF-alpha-induced endothelial expression of both VCAM-1 and ICAM-1 ($P < 0.01$; $P < 0.001$). Both walnut extract (at 10-25 microg/ml) and ellagic acid (at 10- 9-10-

8 m) induced nodule formation in KS483 osteoblasts. These results suggested that the walnut extract has a high anti-atherogenic potential and a remarkable osteoblastic activity, an effect mediated, at least in part, by its major component ellagic acid [125-126].

1.35. *Juniperus oxycedrus*

The arterial blood pressure of normotensive rats was significantly reduced by the iv administration of the methanol and dichloromethanol extracts of *Juniperus oxycedrus*. The hypotensive effect of these extracts was independent of the adrenergic system [127-128].

1.36. *Lantana camara*

The cardiovascular activity of ethanolic extract of *Lantana camara leaves* was evaluated in different experimental models. The ethanolic extract of *Lantana camara leaves* produced negative inotropic and negative chronotropic effect, antagonized by atropine on isolated frog heart. The ethanolic extract caused dose dependent ($p<0.05$) decrease in the mean arterial blood pressure in anesthetic chick. Salt treated rats displayed significant ($p<0.05$) increase in blood level of SGOT, SGPT, creatinine and sodium, decrease in potassium levels in comparison with normal rats. Treatment with ethanolic extract (200 and 400 mg/kg) significantly balanced the ionic levels such as lower the sodium and elevate the potassium levels. Creatinine levels were significantly ($p<0.05$) reduced by ethanolic extract [129-130].

1.37. *Leontice leontopetalum*

Low concentrations of petaline chloride (1-300 micrograms/ml), a quaternary alkaloid from *Leontice leontopetalum,* caused relaxation of the epinephrine-contracted aorta, contraction of the ileum, and no effect on the trachea. It also increased, in a concentration-dependent manner, the contractions of the spontaneously-beating atrium and the isolated perfused heart. These effects were not affected by propranolol but were significantly reduced in the presence of quinacrine, suggesting the participation of arachidonic acid metabolism to this effect. Larger concentrations (up to 3 mg/ml) caused nonsustained large contractions of the aorta and the trachea and increased the amplitude of the phasic contractions of the ileum. The contractile effects were not inhibited by atropine. In anesthetized rats, petaline chloride (0.3-3 mg/100 g body weight; ip) increased both the systolic and diastolic blood pressure and increased the heart rate [131].

Oblongine chloride (3×10^{5}-10^{-3} M), a quaternary alkaloid from *Leontice leontopetalum*, caused concentration-dependent relaxation of guinea-pig isolated ileal longitudinal segments, the effect was not blocked by propranolol (10^{-6} M) alone or in combination with prazosin (3×10^{-8} M), or by indomethacin (10^{-6} M), but was reduced by desensitization of the preparation by prior exposure to a combination of propranolol and yohimbine (3×10^{-6} M). Oblongine chloride ($10^{-5\text{-}3} \times 10^{-3}$) M) also caused concentration-dependent relaxation of epinephrine- precontracted guinea-pig isolated main pulmonary artery rings. The effect was not affected by propranolol or by indomethacin but was significantly attenuated by pretreatment with 3×10^{-5} MATP and potentiated by pretreatment with quinacrine (10^{-5} M). Oblongine chloride (10^{-5} M-3×10^{-3} M) caused concentration-dependent increase in the contractility of guinea-pig atrium, but did not affect the rate of the atrium. It also caused concentration-dependent increase in the contractility of the isolated perfused heart except that large concentrations of oblongine (10^{-3}, 3×10^{-3} M) which inhibited both contractility and rate of the heart. The inotropic effects of oblongine on the atrium were not blocked by propranolol or indomethacin but were significantly blocked by quinacrine [132-133].

1.38. *Lepidium sativum*

The antihypertensive effect of the aqueous extract of *Lepidium sativum* was studied in normotensiveand spontaneously hypertensive rats. Daily oral administration of the aqueous extract (20mg/kg for 3 weeks) caused significant decrease in blood pressure ($p< 0.01$) in hypertensive rats, with no significant change in normotensive rats during the period of treatment. The systolic blood pressure was decreased significantly from the 7^{th} day ($p< 0.05$) to the end of treatment ($p< 0.01$) in hypertensive rats. No significant changes were recorded on heart rate after the aqueous extract treatment in hypertensive and normotensive rats [134-135].

1.39. *Linum usitatissimum*

The antihypertensive activity of ethanolic extract of seeds of *Linum usitatissimum* (200 and400 mg/kg) was investigate in renal artery occlusion (RAO) induced hypertensive rats. RAO significantly increased hemodynamic parameters at 15, 30 and 45 min of clamp removal. Ethanolic extract (400 mg/kg) significantly decreased hemodynamic parameters at 15 min after clamp removal which remained for 60 min. Ethanolic extract (400 mg/kg) treated group also showed significant improvement in left ventricular function at 15, 30 and 45 min of clamp removal. The flow cytometric analysis

showed significant decrease in reactive oxygen species production by renal cells in ethanolic extract (400 mg/kg) treated group as compared with RAO group which indicated antioxidant activity of ethanolic extract [136].

The effects of golden flaxseed grains on blood pressure, anthropometric and oxidative parameters were evaluated in healthy human volunteers. All subjects received 40 gram mixed with water in the morning for a period of 14 days. Oxidative parameters showed significant reductions ($p< 0.05$) in oxidative damage to lipids and proteins. There were no significant differences in anthropometric parameters, blood pressure, DNA damage and micronuclei frequency after 14-day supplementation [137].

The anti-hypertensive effect of aqueous extract with secoisolariciresinol diglucoside (SDG) enriched fraction (SEF) of defatted flaxseeds was evaluated in fructose-induced hypertension in rats. SEF was given orally once daily at the doses of 50, 100 and 200mg/kg. Fructose feeding for 4 weeks induced hypertension, increased triglyceride level and increased plasma glucose levels in rats. The SEF possessed a significant reverse in hypertension by restoring SBP and also significantly reduced high plasma glucose, high cholesterol and triglyceride levels in dose dependent manner. *In vitro* study showed that SEF significantly inhibited angiotensin- converting enzyme (ACE) compared to standard [138].

The hypoglycemic and hypotensive effects of (a standardized *Linum usitatissimum* lignan enriched product, 543 mg) were studied in healthy older adults as an aspect of safety. After 6 months of treatment, no incidents of hypoglycemia or hypotension were observed during flaxseed treatment, suggesting that 543 mg below the concentrations produced observable adverse effect level [139].

The anti- hypertensive activity of flaxseed-supplemented standard diet 10% (FLX) was examined in cyclosporin A-induced hypertensive male rats. Hypertensive rats fed the FLX-supplemented diet had significantly lower blood pressure, improved lipid profile and improved liver and kidney functions (aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, uric acid, creatinine, and rennin)[140].

1.40. *Lycium barbarum*

The anti-hypertensive effect of *Lycium barbarum* was studied in a rat model of salt-sensitive hypertension. Blood pressure was significantly increased in the model ($p< 0.05$). *Lycium barbarum* treatment reversed the elevated blood pressure to normal level. Expression of lncRNA sONE was significantly reduced and eNOS expression level was dramatically improved in the hypertension model rats treated with the *Lycium barbarum* [141].

1.41. *Mangifera indica*

The direct effect of *Mangifera indica* leaf extract was studied in the rabbit myocardium. The results clearly indicated that the leaf extract possesses negative chronotropic and inotropic effects. The author concluded that *Mangifera indica* can be used in patients with hypertension because it significantly lowered the rate and force of contraction of the heart [142-143].

1.42. *Marrubium vulgare*

The crude extracts of the aerial parts of *Marrubium vulgare* were strongly inhibited the *in vitro* KCl-induced contraction of rat aorta. It appeared that furanic labdane diterpenes, marrubenol and marrubiin were the most active compounds [144].

The relaxant activity of marrubenol (a diterpenoid extracted from *Marrubium vulgare*), and the underling mechanism were studied in rat aorta. Marrubenol inhibited the contraction evoked by 100 mM KCl (IC_{50}: 11.8±0.3 microM, maximum relaxation: 93±0.6%) than of the contraction evoked by noradrenaline (maximum relaxation: 30±1.5%) in rat aorta. It also simultaneously inhibited the Ca^{2+} signal and the contraction evoked by 100 mM KCl, and decreased the quenching rate of fura-2 fluorescence by Mn^{2+}.Marrubenol inhibited Ba^{2+} inward current in a voltage-dependent manner (KD: 8±2 and 40±6 microM at holding potentials of -50 and -100 mV, respectively). The results revealed that Marrubenol inhibited smooth muscle contraction by blocking L-type calcium channels [145].

The hypotensive effect of the water extract of *Marrubium vulgare* was investigated in spontaneously hypertensive and in normotensive rats. Oral administration of *Marrubium vulgare* extract lowered the systolic blood pressure of spontaneously hypertensive rats but not in normotensive rats. *Marrubium vulgare* extract inhibited the contractile responses of rat aorta to noradrenaline and to KCl (100 mM). Inhibition was greater in aorta from spontaneously hypertensive rats compared to normotensiverats and was not affected by the NO synthase inhibitor, N-nitro-L-arginine [146].

The effects of 10 week- treatment with amlodipine or *Marrubium vulgare* water extract on systolic blood pressure, cardiovascular remodeling and vascular relaxation were studied in spontaneously hypertensive rats. Both treatments produced similar decrease in systolic blood pressure. Amlodipine treatment reduced left ventricle, aortic and mesenteric artery weight, while, marrubium treatment had a significant antihypertrophic effect in aorta only. Relaxation to acetylcholine (ACh) of mesenteric artery was improved by *Marrubium vulgare* but not by amlodipine treatment [147-148].

1.43. *Melilotus officinalis*

The therapeutic efficacy and the clinical tolerability of an association of alpha tocopherol, rutin, *Melilotus officinalis*, and *Centella asiatica* was evaluated in patients with chronic venous insufficiency after 15 and 30 days treatment. A significant improvement of the clinical symptoms was obtained, characterized by a diminution of the suprafascial edema after the treatment period [149-150].

The safety and outcome of one-week administration of *Melissa officinalis* aqueous extract (50, 100 and 200 mg/kg/day, orally for a week)on blood pressure and ECG parameters were studied in rats. Consumption of *Melissa officinalis* extract associated with prolonged QRS interval ($P< 0.05$ for 50 and 100 mg/kg groups, and $P< 0.01$ for 200 mg/kg group versus the control group, respectively), prolonged QTc and JT intervals ($P< 0.01$ for different doses versus the control group) and prolonged TpTe interval ($P< 0.001$ compared with the control group). However, different doses of the extract had no significant effect on RR interval, PR interval, amplitudes of ECG waves, heart rate and blood pressure [151].

The effects of aqueous extract of *Melissa officinalis* aerial parts on the resistance of the heart to stressful conditions were studied in rats. The extract (50, 100, and 200 mg/kg) significantly reduced the heart rate ($264 \pm 5.2 \pm 5$ and 281 ± 3 versus 377 ± 13 in control group, $P < 0.01$). Blood pressure was significantly decreased in 50mg extract + isoproterenol (ISO) (75 ± 5) versus 50mg extract (110 ± 6) and 100 mg extract + ISO (72 ± 6) versus 100 mg extract (105 ± 5 mmHg, $P<0.01$). The malondialdehyde levels of the injured hearts were lower in 50 mg extract + ISO and 100 mg extract + ISO groups than in the ISO group ($P < 0.05$). Serum cardiac troponin I was higher in the 200 mg extract + ISO group (5.1 ± 1.7) than in the ISO group (2.7 ± 0.7 ng/ml, $P<0.05$) [152].

Vasorelaxant effect of the aqueous extract of *Melissa officinalis* ssp. *officinalis* was investigated on isolated rat aortic rings pre-contracted with phenylephrine. The extract and rosmarinic acid isolated from the extract possessed vasorelaxant effect, the vasorelaxant effect was entirely dependent on the presence of endothelium and was abolished by pretreatment with N (omega)-nitro-L-arginine (L-NAME), whereas pretreatment with indomethacin and glibenclamide reduced the relaxation to a minor extent [153].

1.44. *Mentha longifolia*

The hypotensive effect of the aqueous methanolic extract of *Mentha longifolia,* was studied in normotensive and hypertensive rats. The extract at doses of 500 and 1000 mg/kg orally, exhibited a significant decrease in blood pressure and heart rate of normotensive rats. A significant antihypertensive and negative chronotropic effects were observed at 1000 mg/kg orally, in hypertensive rats [154].

The effects of the extract of *Mentha longifolia* on blood pressure and the possible mechanisms were studied in rats. The crude extract of *Mentha longifolia* and aqueous and chloroform fractions caused a dose dependent fall in mean arterial pressure. Atropine pretreatment abolished the effect of extract and aqueous fraction but did not change that of chloroform fraction. In rat aortic rings, crude extract and aqueous fraction-induced endothelium-dependent atropine-sensitive vasodilator effect. In Guinea pig atrial strips, crude extract and chloroform fraction suppressed force and rate of contractions, similar to verapamil. In rabbit aortic rings, crude extract relaxed phenylephrine (1 μM) and high K^+ (80 mM) pre-treated ring. Chloroform fraction was more potent against high K^+, similar to verapamil and caused a rightward shift in the Ca^{++} concentration-response curves. Aqueous fraction partially relaxed high K^+ pretreated ring [155].

1.45. *Momordica charantia*

The protective effect of *Momordica charantia*was investigated in vascular complications associated diabetes mellitus induced by Streptozotocin in rats. Oral administration of the fruit extract (1.5 g/kg) for 28 days significantly decrease ($P< 0.05$) blood pressure, total cholesterol and triglyceride levels. Aortic tissue NO level was significantly increased and malondialdehyde level was decreased in the extract treated diabetic group. Morphological deterioration of the aortic tissues was reverted to normal in the extract treated diabetic group [156].

The methanol extract of *Momordica charantia*possessedsignificantly higher (IC_{50} = 109.63 µg/ml, P< 0.05) angiotensin-I converting enzyme inhibitory activity than aqueous extract (IC_{50} = 182.95 µg/ml). The methanol extract also significantly showed higher (P < .05)inhibitory effect on Fe^{2+}- and cisplatin-induced lipid peroxidation than aqueous extract [157].

2. Conclusion

Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many pharmaceutical drugs. This review presented an overview of medicinal plants with hypotensive and vascular effects as promising future therapies because of efficacy and safety.

Compliance with ethical standards

Acknowledgments

We would like to thank the college of medicine, University of Thi Qar for support.

References

[1] Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with cardiovascular effects (part 1). Int J of Pharmacology & Toxicology 2015; 5 (3): 163-176.

[2] Al-Snafi AE. Medicinal plants with cardiovascular effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6 (7): 43-62.

[3] Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with hypolipidemic, hemostatic, fibrinolytic and anticoagulant effects (part 1). Asian Journal of Pharmaceutical Science & Technology 2015; 5 (4): 271-284.

[4] Shinde S, Shastry S and Agrawal S L. Cardiovascular effects of aqueous extract of *Adonis vernalis*. IX Annual conference of IPS , 76-77. http://lib.hebust.edu.cn/ywyfzsk/zsk/pharm-docum/b014.pdf

[5] Al-Snafi AE. *Adonis aestivalis*: pharmacological and toxicological activities- A revew. Asian Journal of Pharmaceutical Science & Technology 2016; 6 (2): 96-102.

[6] Al-Snafi AE. The pharmacological and therapeutic importance of *Agrimonia eupatoria*- A review. Asian Journal of Pharmaceutical Science and Technology 2015; 5 (2):112-117.

[7] Al-Qattan KK, Alnaqeeb MA, Ali M *et al.*The antihypertensive effect of garlic (*Allium sativum*) in the rat two-kidney–one-clip Goldblatt model. Journal of Ethnopharmacology 1999; 66: 217-222.

[8] Ali M, Al-Qattan KK, Al-Enezi F *et al.* Effect of allicin from garlic powder on serum lipids and blood pressure in rats fed with a high cholesterol diet. Prostaglandins Leukotrienes and Essential Fatty Acids 2001; 62 (4): 253-259.

[9] Fallon MB, Abrams GA, Abdel-Razek TT *et al.* Garlic prevents hypoxic pulmonary hypertension in rats. Am J Physiol Lung Cell Mol Physiol 1988; 275: L283-L287.

[10] Silagy CA and Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens1994;12: 463-468.

[11] Aqel MB, Gharaibah MN and Salhab AS. Direct relaxant effects of garlic juice on smooth and cardiac muscles. J Ethnopharmacol 1991; 33: 13-19.

[12] Al-Snafi AE. Pharmacological effects of *Allium* species grown in Iraq. An overview. International Journal of Pharmaceutical and health care Research 2013;1 (4):132-147.

[13] Al-Snafi AE. The pharmaceutical importance of *Althaea officinalis* and *Althaea rosea* : A Review. Int J Pharm Tech Res 2013; 5 (3): 1387-1385.

[14] Durate J, Perez-Vizcaino F, Torres AI, Zarzuelo A, Jimenez J and Tamargo J. Vasodilator effects of visnagin in isolated rat vascular smooth muscle. Eur J Pharmacol 1995; 286 (2): 115-122.

[15] Durate J, Vallejo I, Perez – Vizcaino F, Jimenez R, Zarzuelo A and Tamargo J. Effects of visnadine on rat isolated vascular smooth muscles. Planta Med 1997; 63 (3): 233-236.

[16] Durate J, Torres A I and Zarzuelo A. Cardiovacular effects of visnagin on rats. Planta Med 2000; 66 (1): 35- 39.

[17] Rauwald HW, Brehm H and Odenthal KP. Screening of nine vasoactive medicinal plants for their possible calcium antagonist activity. Strategy of selection and isolation for the active principles of *Olea europaea* and *Peucedanaum ostruthium*. Phytotherapy Research 1994; 8: 135-140.

[18] Rauwald HW, Brehm H and Odenthal KP. The involvement of Ca^{2+} channel blocking mode of action in the pharmacology of *Ammi visnaga* fruits. Planta Medica 1994; 60: 101-105.

[19] Erbring H, Uebel H and Vogel G. Zur Chemie, Pharmakologie und Toxicologie von Visnadin. Arzneimittelforschung 1967; 17: 283-287.

[20] Al-Snafi AE. Chemical constituents and pharmacological activities of *Ammi majus* and *Ammi visnaga*. A review. International Journal of Pharmacy and Industrial Research 2013; 3 (3):257-265.

[21] Duarte J, Perez-Vizcaino F, Torres AI, Zarzuelo A, Jimenez J and Tamargo J. Vasodilator effects of visnagin in isolated rat vascular smooth muscle. Eu J Pharmacol 1995; 286 (2):115-122.

[22] Altinterim B. Hıltan tohumunun (Umbelliferae, *Ammi visnaga* L.) düz kaslar üzerine etkisi. Nevşehir Dergisi Üniversitesi Fen Bilimleri Enstitü 2012:60-64.

[23] Leung A Y, Foster S. Encyclopedia of common natural ingredients used in food, drugs and cosmetics. New York, John Wiley and Sons 1996.

[24] Al-Snafi AE. The pharmacological importance of *Anethum graveolens*- A review. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6 (4): 11-13.

[25] African pharmacopoeia. Vol.1. Lagos, Organization of African Unity, Scientific Technical and Research Commission 1985.

[26] Branković, S., Kitić, D., Radenković, M., Veljković, S., Kostić, M., Miladinović, B., & Pavlović, D. Hypotensive and cardioinhibotory effects of the aqueous and ethanol extracts of celery (*Apium graveolens*, Apiaceae). Acta Medica Medianae 2010; 49 (1): 13-16.

[27] Al-Snafi AE. The Pharmacology of *Apium graveolens*- A review. International Journal for Pharmaceutical Research Scholars 2014; 3 (1-1): 671-677.

[28] Quist EE. Peanut *(Arachis hypogaea L.*) as a source of antihypertensive and antimicrobial peptides. PhD thesis, Uga Univ 2005.

[29] Al-Snafi AE. Chemical constituents and pharmacological activities of *Arachis hypogaea* - A review. International Journal for Pharmaceutical Research Scholars 2014; 3 (1-1): 615-623.

[30] Sobotka W, Flis M, Antoszkiewicz Z, Lipiński K and Zduńczyk Z. Effect of oat by-product antioxidants and vitamin E on the oxidative stability of pork from pigs fed diets supplemented with linseed oil. Arch AnimNutr 2012; 66 (1): 27-38.

[31] Andersson KE, Axling U, Xu J, Swärd K, Ahrné S, Molin G, Holm C and Hellstrand P. Diverse effects of oats on cholesterol metabolism in C57BL/6 mice correlate with expression of hepatic bile acid-producing enzymes. Eur J Nutr 2013; 52 (7): 1755-1769.

[32] Othman RA, Moghadasian MH and Jones PJ. Cholesterol-lowering effects of oat β-glucan. Nutr Rev 2011; 69 (6): 299-309.

[33] Maki KC, Galant R, Samuel P, Tesser J, Witchger MS, Ribaya-Mercado JD, Blumberg JB and Geohas J. Effects of consuming foods containing oat beta-glucan on blood pressure, carbohydrate metabolism and biomarkers of oxidative stress in men and women with elevated blood pressure. Eur J ClinNutr 2007; 61 (6): 786-795.

[34] Nie L, Wise ML, Peterson DM and Meydani M. Avenanthramide, a polyphenol from oats, inhibits vascular smooth muscle cell proliferation and enhances nitric oxide production. Atherosclerosis 2006; 186 (2): 260-266.

[35] Al-Snafi AE. The nutritional and therapeutic importance of *Avena sativa* - An overview. International Journal of Phytotherapy 2015; 5 (1): 48-56.

[36] Al-Snafi AE. The Chemical constituents and pharmacological effects of *Bryophyllum calycinum*-A review. Journal of Pharma Sciences and Research 2013; 4 (12): 171-176.

[37] John AO. Ojewole. Antihypertensive properties of *Bryophyllum pinnatum* { (Lam) Oken} leaf extracts. Am J Hypertens 2002; 15: 34A–34A

[38] Prasad AK, Kumar S, Iyer SV, Sudani RJ and Vaidya SK. Pharmacognostical, phytochemical and pharmacological review on *Bryophyllum pinnata.* International Journal of Pharmaceutical & Biological Archives 2012; 3 (3):423-433.

[39] Datté YJ, Traoré A, Offoumou AM. Anti-hypertensive effect of aqueous extract of *Caesalpinia bonduc*)Caesalpiniaceae) on arterial blood pressure in guinea-pig. Revue Med Pharm Afr 1997; 11: 79-88 .

[40] Al-Snafi AE. Pharmacology and medicinal properties of *Caesalpinia crista*- An overview. International Journal of Pharmacy 2015; 5 (2): 71-83.

[41] Zeggwagh NA, Michel JB and Eddouks M. Cardiovascular effect of *Capparis spinosa* aqueous extract. Part VI: *In vitro* vasorelaxant effect. American Journal of Pharmacology and Toxicology 2007; 2 (3): 135-139.

[42] Benzidane N, Imane K, Abderrahmane B, Noureddine C, Seddik K, Xavier N, and Lekhmici A. *In vitro* vasomotor effects of *Capparis spinosa* aqueous extracts. The 3rd International Symposium on the Medicinal Plants, Their Cultuvation and Aspects of Uses , BeitZaman Hotel & Resort, Petra – Jordan, November 21-23/ 2012.

[43] Al-Snafi AE. The chemical constituents and pharmacological effects of *Capparis spinosa* - An overview. Indian Journal of Pharmaceutical Science and Research 2015; 5 (2): 93-100.

[44] Liu F, Wei Y, Yang XZ, Li FG, Hu J and Cheng RF. Hypotensive effects of safflower yellow in spontaneously hypertensive rats and influence on plasma renin activity and angiotensin II level. Yao Xue Xue Bao1992;27 (10): 785-787

[45] Bai Y, Lu P, Han C, Yu C, Chen M, He F and Yi D, Wu L. Hydroxysafflor yellow A (HSYA) from flowers of *Carthamus tinctorius* L. and its vasodilatation effects on pulmonary artery. Molecules 2012; 17 (12): 14918-14927.

[46] Nie PH, Zhang L, Zhang WH, Rong WF and Zhi JM. The effects of hydroxysafflor yellow A on blood pressure and cardiac function. J Ethnopharmacol 2012; 139 (3): 746-750.

[47] Al-Snafi AE. The chemical constituents and pharmacological importance of *Carthamus tinctorius* - An overview. Journal of Pharmaceutical Biology 2015; 5 (3): 143-166.

[48] Al-Snafi AE. Cardiovascular effects of *Carthamus tinctorius*: A mini-review. Asian Journal of Pharmaceutical Research 2015; 5 (3): 199-209.

[49] Zeggwagh NA, Michel JB and Eddouks M. Vascular effects of aqueous extract of *Chamaemelum nobile*: in vitro pharmacological studies in rats. Clin Exp Hypertens 2013; 35 (3): 200-206.

[50] Al-Snafi AE. Medical importance of *Anthemis nobilis* (*Chamaemelum nobilis*)- A review. Asian Journal of Pharmaceutical Science & Technology 2016; 6 (2): 89-95.

[51] Pedroche J, Vioque J, Millan F, Alaiz M, Gir J and Yust MM. Production of ACE inhibitory peptides by digestion of chickpea legumin with alcalase. Food Chemistry2003; 81: 363-369.

[52] Al-Snafi AE. The medical Importance of *Cicer arietinum* - A review. IOSR Journal of Pharmacy 2016; 6 (3): 29-40.

[53] Sakurai N, Iizuka T, Nakayama S, Funayama H, Noguchi M and Nagai M. Vasorelaxant activity of caffeic acid derivatives from *Cichorium intybus* and *Equisetum arvense*. Yakugaku Zasshi 2003; 123 (7):593-598.

[54] Al-Snafi AE. Medical importance of *Cichorium intybus* – A review IOSR Journal of Pharmacy 2016; 6 (3): 41-56.

[55] Yoshikawa M, Matsuda H, Morikawa T, Xie H, Nakamura S and Muraoka O. Phenylethanoid oligoglycosides and acylated oligosugars with vasorelaxant activity from *Cistanche tubulosa*. Bioorg Med Chem 2006; 14 (22):7468-7475.

[56] Al-Snafi AE. Bioactive metabolites and pharmacology of *Cistanche tubulosa*- A review. IOSR Journal of Pharmacy 2020; 10 (1): 37-46.

[57] Ohnishi A, Asayama R, Mogi M, Nakaoka H, Kan-No H, Tsukuda K, Chisaka T, Wang XL, Bai HY, Shan BS, Kukida M, Iwanami J and Horiuchi M. Drinking citrus fruit juice inhibits vascular remodeling in cuff-induced vascular injury mouse model. PLoS One 2015; 10 (2):e0117616.

[58] Akhtar SS. Evaluation of Cardiovascular Effects of *Citrus aurantifolia* (Linn.) Fruit. Social Science Research Network 2013, http://ssrn.com/abstract=2279447

[59] Souza A, Lamidi M, Ibrahim B, Samseny A, Mounanga MB and M'Batchi. B. Antihypertensive effect of an aqueous extract of *Citrus aurantifolia* (Rutaceae) (Christm.) Swingle, on the arterial blood pressure of mammal. International Research of Pharmacy and Pharmacology 2011; 1 (7): 142-148.

[60] Perez YY, Jimenez-Ferrer E, Alonso D, Botello-Amaro CA and Zamilpa A. *Citrus limetta* leaves extract antagonizes the hypertensive effect of angiotensin II. Journal of Ethnopharmacology 2010; 128 (3): 610-614.

[61] Asgary S and Keshvari M. Effects of *Citrus sinensis* juice on blood pressure. ARYA Atheroscler 2013; 9 (1): 98-101.

[62] Kumamoto H, Matsubara Y, Izuka Y, Okamoto K, Yokoi K. Structure and hypotensive effect of flavonoid glycosides in orange (*Citrus sinensis* OSBECK) peelings. Agric Biol Chemistry 1986; 50: 781-783.

[63] Al-Snafi AE. Nutritional value and pharmacological importance of citrus species grown in Iraq. IOSR Journal of Pharmacy 2016; 6 (8): 76-108.

[64] Abuo-Shaaban RR, Angari AA, El-Tahir KE, Al-KhamisKI and Mirghani OM. Comparative hypotensive and respiratory stimulation effects of ripe and unripe fruit mucilage of *Cordia myxa* and *Cordia obliqua* in guineapigs and rabbits. Phytotherapy Res 1989; 3 (4): 126-131.

[65] Al-Snafi AE. The Pharmacological and therapeutic importance of *Cordia myxa*- A review. IOSR Journal of Pharmacy 2016; 6 (6): 47-57.

[66] Jabeen Q, Bashir S, Lyoussi B and Gilani AH. Coriander fruit exhibits gut modulatory, blood pressure lowering and diuretic activities. J Ethnopharmacol 2009;122 (1):123-130.

[67] Al-Snafi AE. A review on chemical constituents and pharmacological activities of *Coriandrum sativum*. IOSR Journal of Pharmacy 2016; 6 (7): 17-42.

[68] Medhin DG, Bakos P and Hadházy P. Inhibitory effects of extracts of *Lupinus termis* and *Coriandrum sativum* on electrically induced contraction of the rabbit ear artery. Acta Pharm Hung 1986; 56 (3): 109-113.

[69] Medhin DG, Hadhazy P, Bakos P and VerzarPetri G.Hypotensive effects of *Lupinus termis* and *Coriandrum sativum* in anesthetized rats: preliminary study. Acta Pharmaceutica Hungarica 1986; 56 (2): 59-63.

[70] Liu N, Yang Y, Mo S, Liao J and Jin J. Calcium antagonistic effects of Chinese crude drugs: Preliminary investigation and evaluation by 45Ca. Applied Radiation and Isotopes 2005; 63:151-155.

[71] Imenshahidi M, Hosseinzadeh H and Javadpour Y. Hypotensive effect of aqueous saffron extract (*Crocus sativus* L.) and its constituents, safranal and crocin, in normotensive and hypertensive rats. Phytother Res 2010; 24 (7): 990-994.

[72] Imenshahidi M, Razavi BM, Faal A, Gholampoor A, Mousavi SM and Hosseinzadeh H. The effect of chronic administration of saffron (*Crocus sativus*) stigma aqueous extract on systolic blood pressure in rats. Jundishapur J Nat Pharm Prod 2013; 8 (4): 175-179.

[73] Mancini A, Serrano-Díaz J, Nava E, D'Alessandro AM, Alonso GL, Carmona M and Llorens S. Crocetin, a carotenoid derived from saffron (*Crocus sativus* L.), improves acetylcholine-induced vascular relaxation in hypertension. J Vasc Res 2014; 51 (5): 393-404.

[74] Al-Snafi AE. The pharmacology of *Crocus sativus*- A review. IOSR Journal of Pharmacy 2016; 6 (6): 8-38.

[75] Kalaivani P, Saranya RB, Ramakrishnan G, Ranju V, Sathiya S, Gayathri V, Thiyagarajan LK, Venkhatesh JR, Babu CS and Thanikachalam S. *Cuminum cyminum*, a dietary spice, attenuates hypertension via endothelial nitric oxide synthase and NO pathway in renovascular hypertensive rats. Clin Exp Hypertens 2013; 35 (7): 534-542.

[76] Al-Snafi AE. The pharmacological activities of *Cuminum cyminum* - A review. IOSR Journal of Pharmacy 2016; 6 (6): 46-65.

[77] Zhou WT, Abdurahman A, Abdusalam E, Yiming W, Abliz P, Aji Q, Issak M, Iskandar G, Moore N and Umar A. Effect of *Cydonia oblonga* Mill. leaf extracts or captopril on blood pressure and related biomarkers in renal hypertensive rats. J Ethnopharmacol 2014; 153 (3): 635-640.

[78] Zhou W, Abdusalam E, Abliz P, Reyim N, Tian S, Aji Q, Issak M, Iskandar G, Moore N and Umar A. Effect of *Cydonia oblonga* Mill fruit and leaf extracts on blood pressure and blood rheology in renal hypertensive rats. J Ethnopharmacol 2014; 152 (3): 464-469.

[79] Al-Snafi AE. The medical importance of *Cydonia oblonga*- A review. IOSR Journal of Pharmacy 2016; 6 (6): 87-99.

[80] Gilani A, Shaheen F and Saeed SA. Cardiovascular action of Daucus carota. Archives Pharmacal Res 1994; 17 (3):150-153·

[81] Al-Snafi AE. Nutritional and therapeutic importance of *Daucus carota*- A review. IOSR Journal of Pharmacy 2017; 7 (2): 72-88.

[82] Gilani AH, Shaheeri F, Saeed SA, Bibi S, Irfanullah, Sadiq M and Faiz S. Hypotensive action of coumarin glycosides from *Daucus carota.* Phytomedicine 2000; 7 (5):423-426.

[83] El Bardai S, Lyoussi B, Wibo M and Morel N. Pharmacological evidence of hypotensive activity of Marrubium vulgare and *Foeniculum vulgare* in spontaneously hypertensive rat.Clin Exp Hypertens 2001; 23 (4):329-343.

[84] Al-Snafi AE. The chemical constituents and pharmacological effects of *Foeniculum vulgare* - A review. IOSR Journal of Pharmacy 2018; 8 (5):81-96.

[85] Mir GN and Ghatak BJ. Pharmacological studies on *Fritillaria imperialis*. L Indian J Exp Biol 1966; 4 (3): 157-160.

[86] Al-Snafi AE. *Fritillaria imperialis*- A review. IOSR Journal of pharmacy 2019, 9 (3): 47-51.

[87] Petkov V. Plants and hypotensive, antiatheromatous and coronarodilating action. Am J Chin Med 1979; 7: 197–236.

[88] Al-Snafi AE. Constituents and pharmacology of *Geum urbanum*- A review. IOSR Journal of pharmacy 2019; 9 (5):28-33.

[89] Mohamed AH, Ali MB, Bashir Ak and Salih AM. Influence of Haplophyllum tuberculatum on the cardiovascular system. Pharmaceutical Biology 2008; 34 (3):213-217.

[90] Al-Snafi AE. Pharmacological importance of *Haplophyllum* species grown in Iraq- A review. IOSR Journal of Pharmacy 2018;8 (5): 54-62.

[91] Kate IE and Lucky OO. The effects of aqueous extracts of the leaves of *Hibiscus rosa-sinensis* Linn. on renal function in hypertensive rats. African Journal of Biochemistry Research 2010; 4 (2): 43-46.

[92] Al-Snafi AE. Chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis*-A review. IOSR Journal of Pharmacy 2018; 8 (7): 101-119.

[93] Sarr M, Ngom S, Kane MO, Wele A, Diop D, Sarr B, Gueye L, Andriantsitohaina R and Diallo AS. In vitro vasorelaxation mechanisms of bioactive compounds extracted from *Hibiscus sabdariffa* on rat thoracic aorta. Nutr Metab (Lond) 2009;6:45. doi: 10.1186/1743-7075-6-45.

[94] Al-Snafi AE. Pharmacological and therapeutic importance of *Hibiscus sabdariffa*- A review. International Journal of Pharmaceutical Research 2018; 10 (3): 451-475.

[95] Onyenekwe PC, Ajani EO, Ameh DA and Gamaniel KS. Antihypertensive effect of roselle (*Hibiscus sabdariffa*) calyx infusion in spontaneously hypertensive rats and a comparison of its toxicity with that in Wistar rats.Cell Biochem Funct 1999; 17 (3): 199-206.

[96] Mojiminiyi FB, Dikko M, Muhammad BY, Ojobor PD, Ajagbonna OP, Okolo RU, Igbokwe UV, Mojiminiyi UE, Fagbemi MA, Bello SO and Anga TJ. Antihypertensive effect of an aqueous extract of the calyx of *Hibiscus sabdariffa*.Fitoterapia 2007;78 (4):292-297.

[97] Mojiminiyi FB, Audu Z, Etuk EU and Ajagbonna OP. Attenuation of salt-induced hypertension by aqueous calyx extract of *Hibiscus sabdariffa*. Niger J Physiol Sci 2012;27 (2):195-200.

[98] Odigie IP, Ettarh RR and Adigun SA. Chronic administration of aqueous extract of *Hibiscus sabdariffa* attenuates hypertension and reverses cardiac hypertrophy in 2K-1C. hypertensive rats. J Ethnopharmacol 2003;86 (2-3):181-185.

[99] Inuwa I, Ali BH, Al-Lawati I, Beegam S, Ziada A and Blunden G. Long-term ingestion of Hibiscus sabdariffa calyx extract enhances myocardial capillarization in the spontaneously hypertensive rat.Exp Biol Med (Maywood) 2012;237 (5):563-569.

[100] Abubakar MG, Ukwuani AN and Mande UU. Antihypertensive activity of *Hibiscus sabdariffa* aqueous calyx extract in albino rats. Sky Journal of Biochemistry Research 2015;. 4 (3):16 – 20.

[101] Ali MB, Salih WM, Mohamed AH and Homeida AM. Investigation of the antispasmodic potential of *Hibiscus sabdariffa* calyces.J Ethnopharmacol 1991; 31 (2): 249-57.

[102] Harera-Arellano A, Flores-Romero S, Chavez-Soto MA and Tortoriello J. Effectiveness and tolerability of a standardized extract from *Hibiscus sabdariffa* in patients with mild to moderate hypertension: A controlled and randomized clinical trial. Phytomedicine 2004; 11 (5): 375-382.

[103] Sudan P, Behl T, Sharma S and Sabharwa S. Treatment of hypertension with *Hibiscus sabdariffa* in Diabetes type-II patients. The Pharmaceutical and Chemical Journal 2014; 1 (3):25-27.

[104] McKay DL, Chen O, Saltzman E and Blumberg JB. *Hibiscus sabdariffa* L. Tea (Tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. J Nutr 2010; 140: 298–303.

[105] Joven J, March I, Espinel E, Fernández-Arroyo S, Rodríguez-Gallego E, Aragonès G, Beltrán-Debón R, Alonso-Villaverde C, Rios L, Martin-Paredero V, Menendez JA, Micol V, Segura-Carretero A and Camps J. *Hibiscus sabdariffa* extract lowers blood pressure and improves endothelial function.Mol Nutr Food Res 2014;58 (6):1374-1378.

[106] Clinical effects produced by a standardized herbal medicinal product of *Hibiscus sabdariffa* on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial.Planta Med 2007;73 (1):6-12.

[107] Nwachukwu DC, Aneke EI, Nwachukwu NZ, Azubike N and Obika LF. Does consumption of an aqueous extract of *Hibscus sabdariffa* affect renal function in subjects with mild to moderate hypertension? J Physiol Sci 2017;67 (1):227-234.

[108] Jonadet M, Bastide J, Bastide P, Boyer B, Carnat AP and Lamaison JL. In vitro enzyme inhibitory and in vivo cardioprotective activities of hibiscus (*Hibiscus sabdariffa* L.). J Pharm Belg 1990;45 (2):120-124.

[109] Aliyu B, Oyeniyi YJ, Mojiminiyi FB, Isezuo SA and Alada AR. The aqueous calyx extract of *Hibiscus sabdariffa* lowers blood pressure and heart rate via sympathetic nervous system dependent mechanisms.Niger J Physiol Sci 2014;29 (2):131-136.

[110] Ojeda D, Jiminez-Ferrer E, Zamilpa A, Harrera-Arellano A, Tortoriello J and Alvarez L. Inhibition of angiotensin convertin enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from *Hibiscus sabdariffa*. Journal of Ethnopharmacology 2010; 127: 7-10.

[111] Olatunji LA, Adebayo JO, Adesokan AA, Olatunji VA and Soladoye AO. Chronic administration of aqueous extract of *Hibiscus sabdariffa* enhances Na^+ -K^+ -ATPase and Ca^{2+} - Mg^{2+}-ATPase activities of rat heart. Pharmaceutical Biology 2006; 44 (3): 213-216.

[112] Ajay M, Chai HJ, Mustafa AM, Gilani AH and Mustafa MR. Mechanism of antihypertensive effects of *Hibiscus sabdariffa* L. calyces. Journal of Ethnopharmacology 2006; 109: 388-393.

[113] Adegunloye BJ, Omoniyi JO, Owolabi OA, Ajagbonna OP, Sofola OA and Coker HA. Mechanisms of the blood pressure lowering effect of the calyx extract of *Hibiscus sabdariffa* in rats.Afr J Med Med Sci 1996;25 (3):235-238.

[114] Nwachukwu DC, Aneke EI, Obika LF and Nwachukwu NZ. Effects of aqueous extract of Hibiscus sabdariffa on the renin-angiotensin-aldosterone system of Nigerians with mild to moderate essential hypertension: A comparative study with lisinopril. Indian J Pharmacol 2015;47 (5):540-545.

[115] Jiménez-Ferrer E, Alarcón-Alonso J, Aguilar-Rojas A, Zamilpa A, Jiménez-Ferrer C I, Tortoriello J and Herrera-Ruiz M. Diuretic effect of compounds from *Hibiscus sabdariffa* by modulation of the aldosterone activity.Planta Med 2012; 78 (18): 1893-1898.

[116] Khan AU and Gilani AH. Cardiovascular inhibitory effects of Hyoscyamus niger.Methods Find Exp Clin Pharmacol 2008;30 (4):295-300.

[117] Al-Snafi AE. Therapeutic importance of *Hyoscyamus* species grown in Iraq (*Hyoscyamus albus*, *Hyoscyamus niger* and *Hyoscyamus reticulates*)- A review. IOSR Journal of Pharmacy 2018; 8 (6):18-32.

[118] Apaydin S, Gldeli E, Karamenderes C, Meral G, Zeybek U and Tuglular I. The Inhibitory effect of *Hypericum triquetrifolium* Turra extract on rat aortic smooth muscle contraction. T Klin J Med Res 2001; 19: 24-30.

[119] Al-Snafi AE.Chemical constituents and pharmacological effects of *Hypericum triquetrifolium*. Indo Am J P Sc 2018; 5 (3): 1757-1765.

[120] Kunhachan P, Banchonglikitkul C, Kaisongkram T, Khayungarnnawee A and Leelamanit W. Chemical Composition, Toxicity and Vasodilatation Effect of the Flowers Extract of *Jasminum sambac* (L.) Ait. "G. Duke of Tuscany". Evid Based Complement Alternat Med 2012; 2012: 471312. . doi: 10.1155/2012/471312

[121] Al-Snafi AE. Pharmacological and therapeutic effects of *Jasminum sambac*- A review. Indo Am J P Sc 2018; 5 (3): 1766-1778.

[122] Ros E, Núñez I, Pérez-Heras A, Serra M, Gilabert R, Casals E and Deulofeu R. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. Circulation 2004;109 (13):1609-1614.

[123] Joukar S, Ebrahimi S, Khazaei M, Bashiri A, Shakibi MR, Naderi V, Shahouzehi B and Alasvand M. Co-administration of walnut (Juglans regia) prevents systemic hypertension induced by long-term use of dexamethasone: a promising strategy for steroid consumers. Pharm Biol 2017;55 (1):184-189.

[124] Oguwike FN, Ebede S and Offor CC. Evaluation of Efficacy of Walnut (Juglans Nigra) On Blood Pressure, Haematological and Biochemical Profile of Hypertensive Subjects. IOSR Journal of Dental and Medical Sciences 2014; 13 (10):75-79.

[125] Papoutsi Z, Kassi E, Chinou I, Halabalaki M, Skaltsounis LA and Moutsatsou P. Walnut extract (Juglans regia L.) and its component ellagic acid exhibit anti-inflammatory activity in human aorta endothelial cells and osteoblastic activity in the cell line KS483. Br J Nutr 2008;99 (4):715-722.

[126] Al-SnafiAE. Chemical constituents, nutritional, pharmacological and therapeutic importance of *Juglans regia*- A review. IOSR Journal of Pharmacy 2018; 8 (11): 1-21.

[127] Bello R, Moreno L, Beltran B, Primo Yufera E. and Esplugues J. Effects on arterial blood pressure of methanol and dichloromethanol extracts from Juniperus oxycedrus L. Phytotherapy Research 1997; 11 161-162.

[128] Al-Snafi AE. Medical importance of *Juniperus communis* - A review. Indo Am J P Sc 2018; 5 (3): 1979-1792.

[129] Matta VK, Pasala PK, Netala S, Pandrinki S and Konduri P. Anti hypertensive activity of the ethanolic extract of *Lantana camara* leaves on high salt loaded Wistar albino rats. Pharmacognosy Journal 2015;7 (5): 289-295.

[130] Al-Snafi AE. Chemical constituents and pharmacological activities of *Lantana camara*- A review. Asian J Pharm Clin Res 2019; 12912):10-20.

[131] Abdalla S, Abu-Zarga M and Sabri S. Preliminary observations on the pharmacology of petaline chloride, a quaternary alkaloid from *Leontice leontopetalum*. Gen Pharmacol 1989; 20 (5): 565-569.

[132] Abdalla S, Zarga MA and Sabri S. Effects of oblongine chloride, an alkaloid from *Leontice leontopetalum* on guinea-pig isolated smooth muscle and heart. General Pharmacology 1993; 24 (2): 299-304.

[133] Al-Snafi AE. Constituents and pharmacological effects of *Leontice leontopetalum*- A review. To Chemistry Journal 2019; 3: 103-108.

[134] Maghrani M, Zeggwagh NA, Michel JB and Eddouks M. Antihypertensive effect of *Lepidium sativum* L. in spontaneously hypertensive rats. J Ethnopharmacol 2005; 100 (1-2): 193-197.

[135] Al-Snafi AE. Chemical constituents and pharmacological effects of *Lepidium sativum*- A review. International Journal of Current Pharmaceutical Research 2019; 11 (6):1-10.

[136] Ghule AE, Jadhav SS and Bodhankar SL. Effect of ethanolic extract of *Linum usitatissimum* on hemodynamic change and left ventricular function renal artery occluded in renovascular hypertension in rat. Pharmacologia 2012; 3 (8): 283-290.

[137] Zuravski L, Coelho RP, Duarte JA, Rocha MO, Mezzomo J, Pilar BC, Galarça LL, Athayde ML, Boligon AA, Machado MM and Manfredini V. Protective role of golden flaxseed (*Linum usitatissimum* L.) against oxidative damage in lipids and proteins of healthy volunteers. Journal of Biosciences and Medicines 2015; 3: 45-53.

[138] Gokhale S and Sahu AN. Effect of aqueous extract of defatted flaxseeds (*Linum usitatissimum* Linn) on fructose-induced hypertension in rats by inhibiting angiotensin-converting enzyme (ACE). IOSR Journal of Pharmacy and Biological Sciences 2016; 11 (6): 53-58.

[139] Billinsky J, Glew RA, Cornish SM, Whiting SJ, Thorpe LU, Alcorn J, Paus-Jenssen L, Hadjistavropoulos T and Chilibeck PD. No evidence of hypoglycemia or hypotension in older adults during 6 months of flax lignan supplementation in a randomized controlled trial: a safety evaluation. Pharm Biol 2013; 51: 778-782.

[140] Al-Bishri WM. Favorable effects of flaxseed supplemented diet on liver and kidney functions in hypertensive Wistar rats. J Oleo Sci 2013; 62: 709-715.

[141] Zhang X, Yang X, Lin Y, Suo M, Gong L, Chen J and Hui R. Anti-hypertensive effect of *Lycium barbarum* L. with down-regulated expression of renal endothelial lncRNA sONE in a rat model of salt-sensitive hypertension. Int J Clin Exp Pathol 2015; 8 (6): 6981-6987.

[142] Gerald GS. Evaluation of the pharmacological activity and phytochemical profile of *Mangifera indica*. MSc thesis. Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi 2012.

[143] Al-Snafi AE, Ibraheemi ZAM, Talab TA. A review on components and pharmacology of *Mangifera indica*. International Journal of Pharmaceutical Research 2021; 13 (2): 3043- 3066.

[144] El Bardai S, Morel N, Wibo M, Fabre N, Llabres G, Lyoussi B and Quetin-Leclercq J. The vasorelaxant activity of marrubenol and marrubiin from *Marrubium vulgare*.Planta Med 2003; 69 (1): 75-77.

[145] El-Bardai S, Wibo M, Hamaide MC, Lyoussi B, Quetin-Leclercq J and Morel N. Characterisation of marrubenol, a diterpene extracted from *Marrubium vulgare*, as an L-type calcium channel blocker. Br J Pharmacol 2003; 140 (7): 1211-1216.

[146] El Bardai S, Lyoussi B, Wibo M and Morel N. Pharmacological evidence of hypotensive activity of *Marrubium vulgare* and *Foeniculum vulgare* in spontaneously hypertensive rat.Clin Exp Hypertens 2001; 23 (4): 329-343.

[147] El Bardai S, Lyoussi B, Wibo M and Morel N. Comparative study of the antihypertensive activity of *Marrubium vulgare* and of the dihydropyridine calcium antagonist amlodipine in spontaneously hypertensive rat.Clin Exp Hypertens 2004; 26 (6): 465-474.

[148] Al-Snafi AE. Al-Saedy HA , Talab TA, Majid WJ, El-Saber Batiha G, Jafari-Sales Abolfazl. The bioactive ingredients and therapeutic effects of *Marrubium vulgare* - A review. International Journal of Biological and Pharmaceutical Sciences Archive 2021; 1 (2):9–21.

[149] Cataldi A, Gasbarro V, Viaggi R, Soverini R, Gresta E and Mascoli F. Effectiveness of the combination of alpha tocopherol, rutin, melilotus, and *Centella asiatica* in the treatment of patients with chronic venous insufficiency.Minerva Cardioangiol 2001; 49 (2): 159-163.

[150] Al-Snafi AE. Chemical constituents and pharmacological effects of *Melilotus officinalis*- A review. IOSR Journal of Pharmacy 2020; 10 (1):26-36.

[151] Joukar S and Asadipour H. Evaluation of *Melissa officinalis* (lemon balm) effects on heart electrical system. Res Cardiovasc Med 2015;4 (2):e27013.

[152] Joukar S, Asadipour H, Sheibani M, Najafipour H and Dabiri S. The effects of *Melissa officinalis* (lemon balm) pretreatment on the resistance of the heart to myocardial injury. Pharm Biol 2016;54 (6):1005-1013.

[153] Ersoy S, Orhan I, Turan NN, Sahan G, *et al*. Endothelium-dependent induction of vasorelaxation by *Melissa officinalis* L. ssp. *officinalis*in rat isolated thoracic aorta. Phytomedicine 2008; 15 (12): 1087-1092.

[154] Akhtar AMS, Jabeen Q, Bashir S, Malik MNH, Khan HU, Rahman MSU, Salma U, Mazhar U, Khan AQ and Islam M. Antihypertensive and toxicity studies of aqueous methanolic extract of *Mentha longifolia* L. The Journal of Animal & Plant Sciences 2013; 23 (6): 1622-1627.

[155] Shah AJ, Bukhari IA and Gilani AH. *Mentha longifolia* lowers blood pressure in anesthetized rats through multiple pathways. Bangladesh J Pharmacol 2016; 11: 784-792.

[156] Abas R, Othman F and Thent ZC. Effect of *Momordica charantia* fruit extract on vascular complication in type 1 diabetic rats.EXCLI J 2015; 14: 179-189.Shodehinde SA, Adefegha SA, Oboh G, Oyeleye SI, Olasehinde TA, Nwanna EE, Adedayo BC and Boligon AA. Phenolic composition and evaluation of methanol and aqueous extracts of bitter gourd (*Momordica charantia* L) leaves on angiotensin-I-converting enzyme and some pro-oxidant-induced lipid peroxidation *in vitro*.J Evid Based Complementary Altern Med 2016; 21 (4): NP67-NP76.