Cardioactive Agents from Plants

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Abstract: This review presents 201 compounds isolated and identified from plants that present cardioactive activity. These substances have been classified by chemical groups and each provides the most relevant information of its pharmacological activity, action mechanism, chemical structure, spectroscopic date and other properties. Chemical structures have been drawn to indicate the stereochemistry. In this review the summary of the scientific information of plants that present biological activity and the compounds responsible for this activity is presented, which introduces the reader to the study of medicinal plants and also provide bibliographic references, where a detailed study of pharmacology can be found.

Key Words: Hypertensive, heart disease, bradycardiac, antiarrhythmic, thrombosis, vasorelaxing.

INTRODUCTION

In recent years there has been a notable increase in medicinal plant consumption in the world. This is because in some cases they have proven to be effective in treating certain, diseases, along with the fact that there is a misperception that they are safe to use. Medicinal plants behave as genuine drugs and some of their chemical constituents have biological activity in humans.

The first significant contribution of folk medicine is the isolation of alkaloids from Sarpagantha (*Rouwolfia serpentina*) who has anti-hypertension and insomnia properties. This was the first ancient-modern relationship in the study of Ayurvedic plants. Progressive developments in chemistry and biology, has led to the study of biological activities of natural products and the search for new drugs from plants for treatment of hypertension. Recently, many plants have been studied because their constituents show promising inhibitory effects of angiotensin (a converting enzyme), thereby suggesting cardiovascular effects.

However, current success in treatment of hypertension, atherosclerosis and ischemic heart disease is due to recent drug discoveries, although definitive cure of patients has not yet been reached. Use of reserpine, an effective drug of plant origin used against hypertension, led scientists to study the chemical compounds associated with its structure. Traditional medical knowledge, seems to indicate further the specificity of their healing.

Interest in research and development of traditional folk medicine, along with research in its ethnographic and psychosocial aspects is recognized and promoted by the World Health Organization [1]. In this review a comprehensive description of the chemical constituents and the biological activities is presented and a critical appraisal of the ethnopharmacological issues is included in view of the many recent findings of importance on this cardioactive plants. The phytochemistry and pharmacological actions of plant components suggest a wide range of clinical applications for the treatment and prevention of heart disease.

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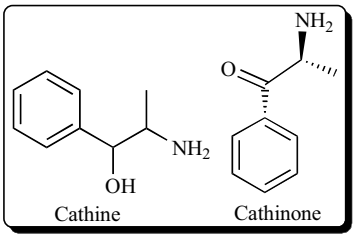
ALKALOIDS AND NITROGEN COMPOUNDS



Found in *Catha edulis* (Khat) (Celastraceae). Both alkaloids produced an increase in the blood pressure and heart rate of the anaesthetized rats [2].

Curine showed vasodilator effect in the rat small mesenteric arteries. The inhibition of influx of calcium ions through voltage-operated calcium channels and non-selective channels, and mobilization of intracellular calcium stores sensitive to nor-adrenaline are involved in the vasodilator effect of curine [3]. In another study higenamine, a benzyltetrahydroisoquinoline alkaloid of the roots of *Aconitum japonicum* (Ranunculaceae), showed anti-platelet and anti-thrombotic effects. Higenamine showed inhibitory activities to both human and rat platelet aggregation induced by ADP, collagen and epinephrine. The anti-thrombotic effects of higenamine were also observed in both mouse acute thrombosis model and rat arterio-venous shunt (AV-shunt) models [4]. Hypoxanthine-9-L-arabinofuranoside found in *Boerhaavia diffusa* (Nyctaginaceae) has been shown to possess relaxed isolated coronary artery strips of the goat contracted with potassium in a concentration dependent manner [5].

Kukoamine found in *Microcystis aeroginosa* (Chroococcaceae) showed antihypertensive activity [6]. Laurotetanine isolated from the leaves of *Laurelia sempervirens* (Monimiaceae), has been widely investigated that produced a hy-

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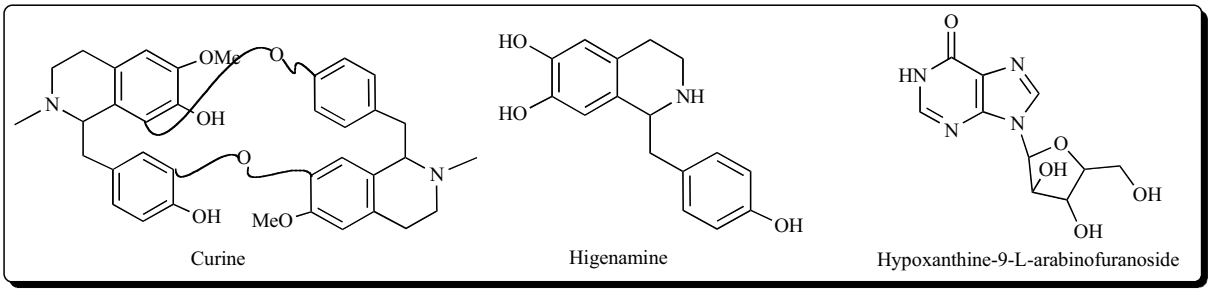
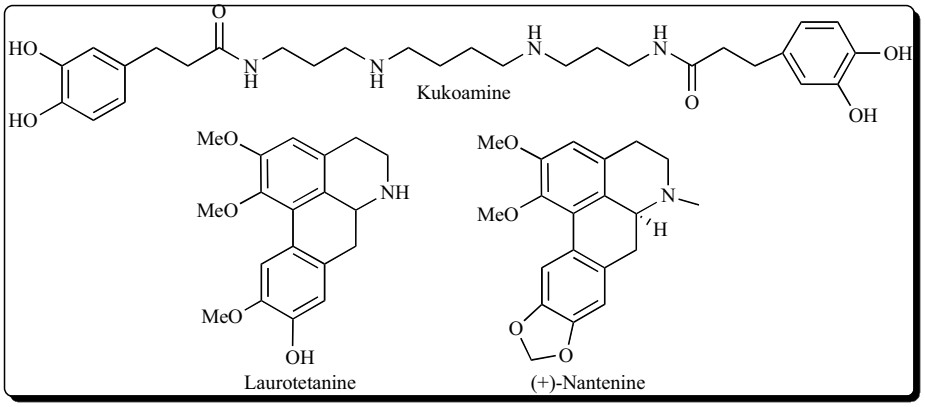


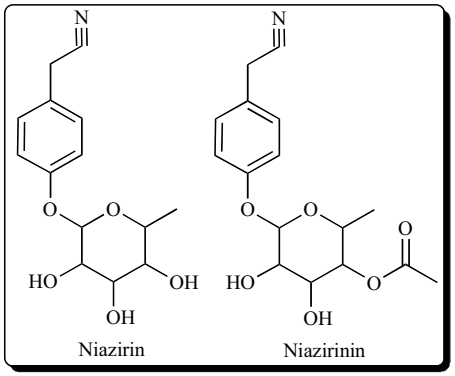
potensive response of -29.0% ± 2.1% in the mean blood pressure of normotensive rats, with a duration of 2 min [7]. In addition (+)-Nantenine, an alkaloid isolated from *Platycapnos spicata* showed potential vasorelaxant activity in rat aorta. Dose of 3-30 μM totally relaxed, in a concentration-dependent manner [8].

Protein

Soybean protein hydrolysate was prepared by peptic hydrolysis. Long-term administration of soybean protein hydrolysate might retard the development of hypertension in hypertensive rats by its inhibitory effect on angiotensin-converting enzyme *in vivo* [12].



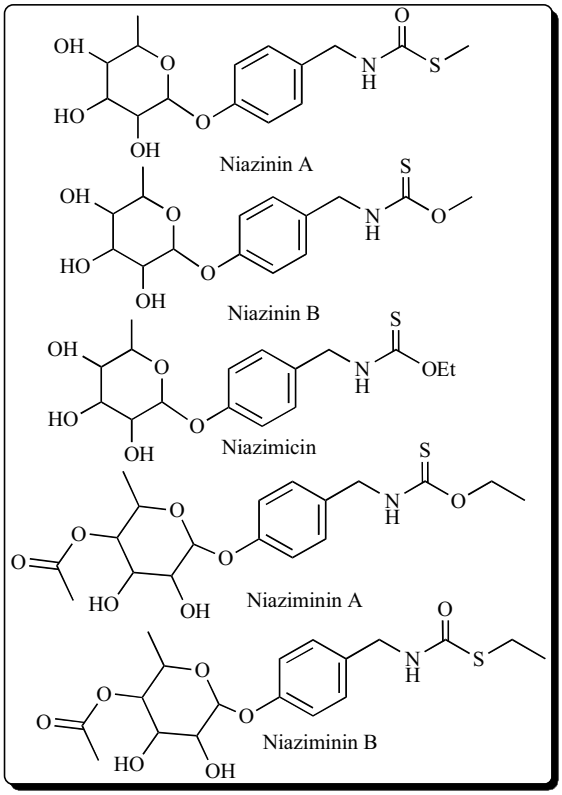
Found in *Aforinga oleifera* (Moringaceae) leave, showed hypotensive activity [9].



Found in the ethanol extract of *Maringa aleifera* (Moringaceae) leaves. Intravenous administration of either one of the compounds (1-10 mg/kg) produced hypotensive and bradycardiac effects in anaesthetized rats. In isolated guinea-pig atria all the compounds (50-150 μg/mL) produced negative inotropic and chronotropic effects [10].

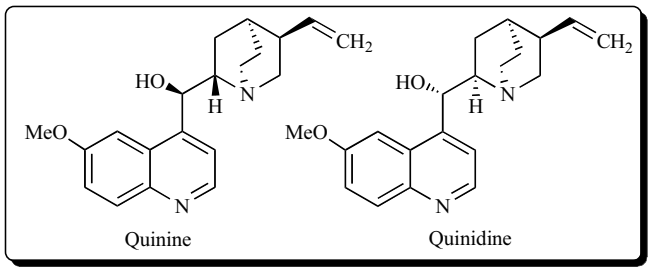
Peptides IY, RIY, VW and VWIS

Four potent angiotensin were isolated from subtilisin digest of rapeseed protein. All isolated peptides lowered blood pressure of spontaneously hypertensive rats (SHR) following oral administration [11].



Protein

Leaf protein containing approximately 50% rubisco (ribulose bisphosphate carboxylase/oxygenase) was obtained from fresh spinach leaf. Pepsin and pepsin-pancreatin digests of spinach leaf protein have potent angiotensin-I Dose of 3-30 μM totally relaxed, in a concentration-dependent manner [13].

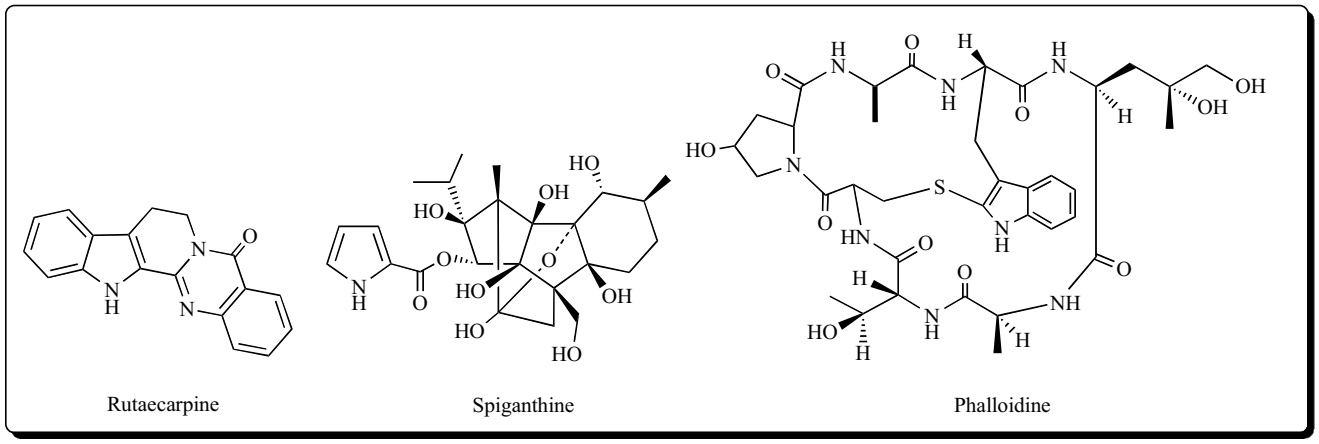


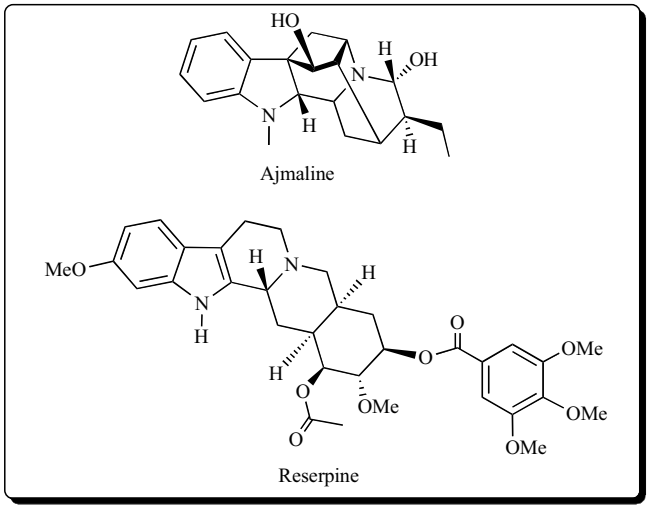
Quinine is one of the most interesting constituents of cinchona bark (*Cinchona officinalis*, Rubiaceae) was discovered to be responsible for this beneficial cardiac effect. Quinidine, a compound produced from quinine, is still used in cardiology today, sold as a prescription drug for arrhythmia. [14].

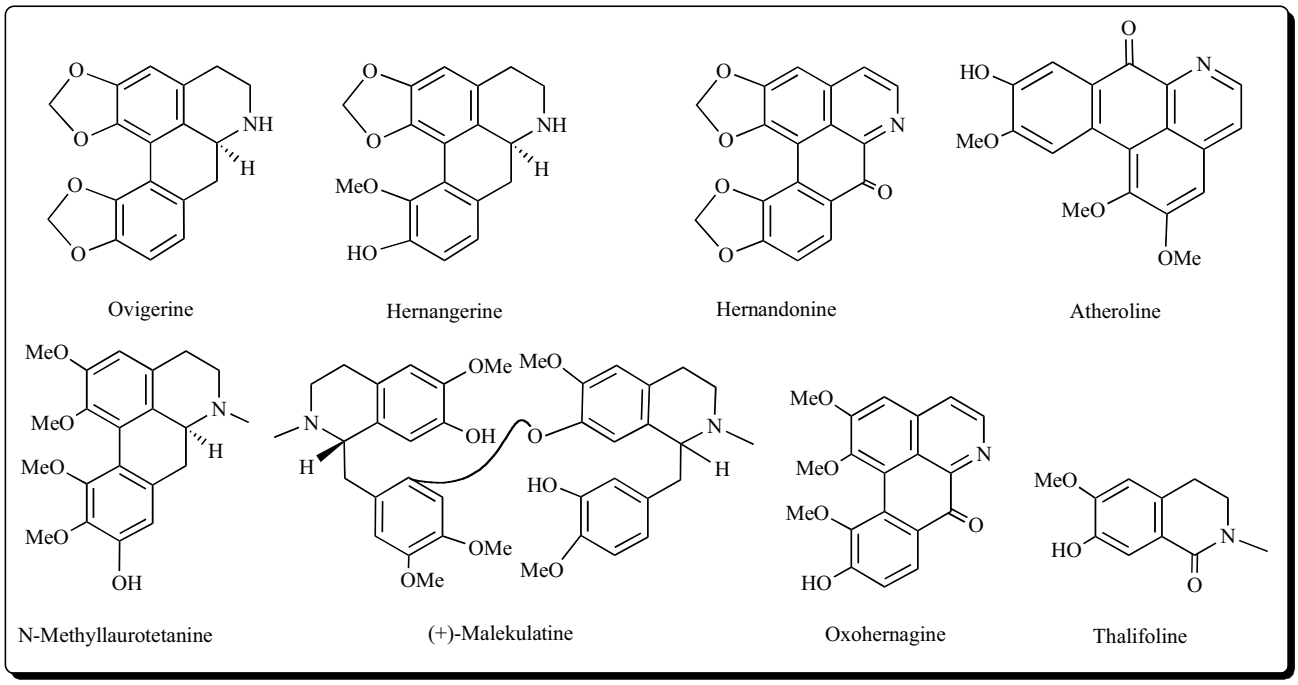
Rutaecarpine was isolated from fruit of *Evodia rutaecarpa* Bentham (Rutaceae). Their properties have been widely investigated as depressor and vasodilator effects activating the vanilloid receptors to evoke calcitonin gene-related peptide (CGRP) release. The depressor and vasodilator effects of rutaecarpine are related to the stimulation of endogenous CGRP release *via* activation of vanilloid receptors in rats [15]. Achenbach and coworkers demonstrate that the spiganthine found in *Spigelia anthelmia* L. (Loganiaceae) showed cardiactive properties [16]. *Amantia phalloides* (Agaricaceae) was found to contain phalloidine, which showed antihypertensive action on urethane anesthetized rats [6].

The Indian *Rauvolfia serpentine* (Apocinaceae) has been since the Vedic and Ayurvedic period the most important medicinal plant for a wide range of phytotherapeutic applications. The therapeutical value of the antiarrhythmic alkaloid ajmaline was established and the use of reserpine as an antihypertensive and neuroleptic drug was clearly defined both alkaloids became important drugs on the general pharmaceutical market. A new enzyme, 1.2-dihydrovomilenine reductase has been detected in *Rauvolfia* cell suspension cultures. The enzyme specifically converts 2β(R)-1,2-dihydrovomilenine through an NADPH-dependent reaction into 17-O-acetylnorajmaline, a close biosynthetic precursor of the antiarrhythmic alkaloid ajmaline from *Rauvolfia* [17].

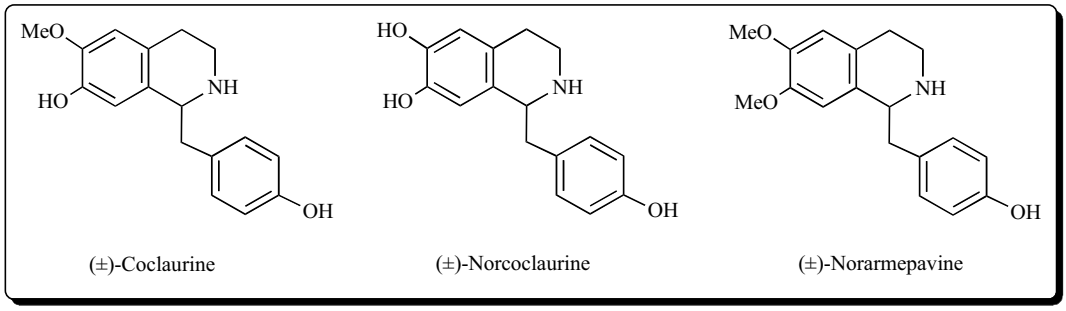
All these alkaloids, have been isolated from the trunk bark of *Hemandia nymphaeifolia* (hernandiaceae). Norapophines as ovigerine, laurotetanine and hernangerine showed marked inhibition of aortic contractions caused by high K^+ (80 mM) and norepinephrine (3 μM), but the vasorelaxing effects of their corresponding oxo-aporphines as hernandonine, atheroline and oxohernangerine were reduced. Moreover, ovigerine showed significant inhibition on aortic contractions induced by high K^+ and norepinephrine, but its dimer, ovigeridimerine, lost vasorelaxing effects. In addition Hernangerine showed marked inhibitory activity on aortic contractions induced by high K^+ and norepinephrine, but hernovine showed reduced inhibitory activity due to the effect of 1,2-methylenedioxy substitution. These findings suggest that among oxoaporphines with 10-hydroxy substitution, showed marked inhibitory activity on aortic contractions induced by K^+ and norepinephrine [18].





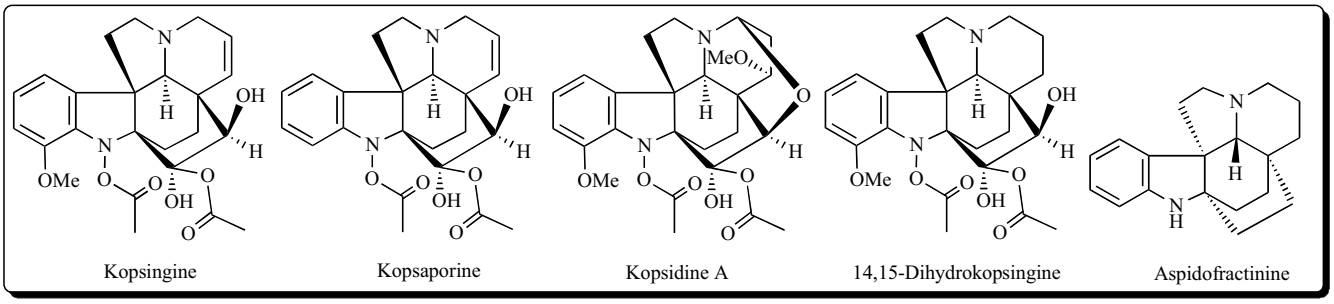


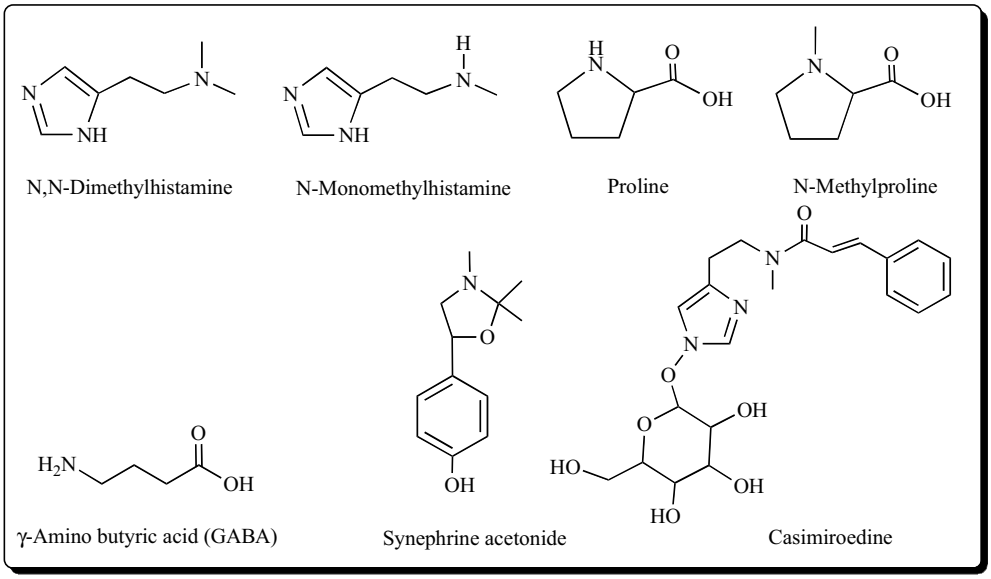
All these alkaloids, showed cardiovascular effects on anaesthetized rats *in vivo*, on spontaneously beating atria and on aortic smooth muscle. In aorta, the effects of (±)-coclaurine and (±)-norcoclaurine, (±)-norarmepavine (10 mg/kg i.v.) decreased the mean arterial pressure and heart rate by 45% and 21 %, respectively, showed a negative chronotropic effect on rat-isolated atria, decreasing the spontaneous frequency by about 54%. These results point to the importance of methylation in these compounds [19]. These alkaloids were isolated from *Xylopia papuana* (Annonaceae) and *Alseodaphne archboldiana* (Lauraceae).



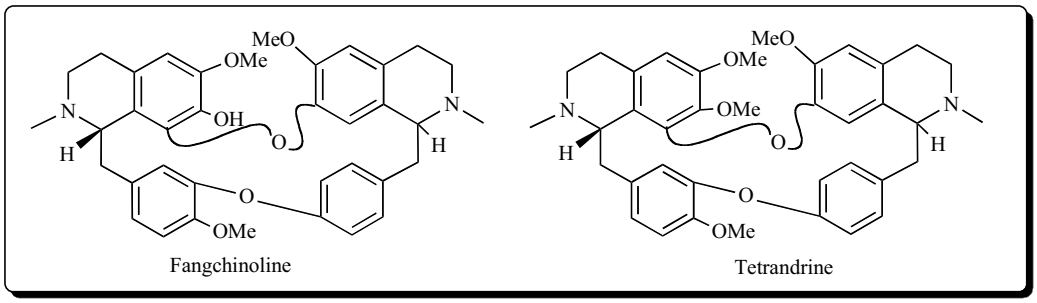
The effect hypotensive of *Kopsia teoi*, (Apocynaceae) has been studied by several authors [20]. Intravenous injection of the aspidofractinine alkaloid, kopsingine (0.2-10.0 mg/kg) produced dose-related decreases in the mean arterial blood pressure and heart rate in anesthetized spontaneously hypertensive rats, which were similar to those seen in normotensive controls.

So reported that in anesthetized rats, histamine derivatives produced transient hypotension mediated *via* H_1-histaminergic receptors and in the case of N,N-dimethylhistamine, *via* nitric oxide release. Synephrine acetonide pro-





duced transient hypertension and tachycardia, mediated *via* α- and β- adrenergic receptors, respectively. Finally, casimiroedine did not modify the blood pressure of anesthetized rats, but lowered it persistently in anesthetized guinea pigs. It was concluded that hypotension produced by *Casimiroa edulis* (Rutaceae) is due to several active components. The immediate effect can be attributed to the histamine derivatives acting on H_1-receptors [21].



Two major components of the Radix of *Stephannia tetrandrae*, have been shown to possess inhibited high K^+ (65.4 mM) and induced sustained contraction in the rat aorta smooth muscle strips and this inhibition was antagonized by increasing the Ca^{2+} concentration in the medium. Tetrandrine possesses antihypertensive and antiarrhythmic effects, was more potent than fangchinoline in blocking calcium channels and antihypertensive activity [22].

Found in *Ephedra* spp. (Ephedraceae). Showed antihypertensive activity [6].

Found in *Uncaria sinensis* (Rubiaceae). Showed antihypertensive activity [6].

These compounds are bisbenzylisoquinoline alkaloid derivatives isolated from Chinese traditional medicine *Menispermum dauricum* DC (Menispermaceae). Dauricine showed antiarrhythmic effects blocked the cardiac transmembrane Na^+, K^+ and Ca^{2+} ion currents and prolonged APD in a normal use-dependent manner in experimental studies. The antiarrhythmic effect of daurisoline is more potent than that of dauricine. In addition, neferine, was isolated from *Nelumbo nucifera* Gaertn, also with antiarrhythmic activity [23].

COUMARINS

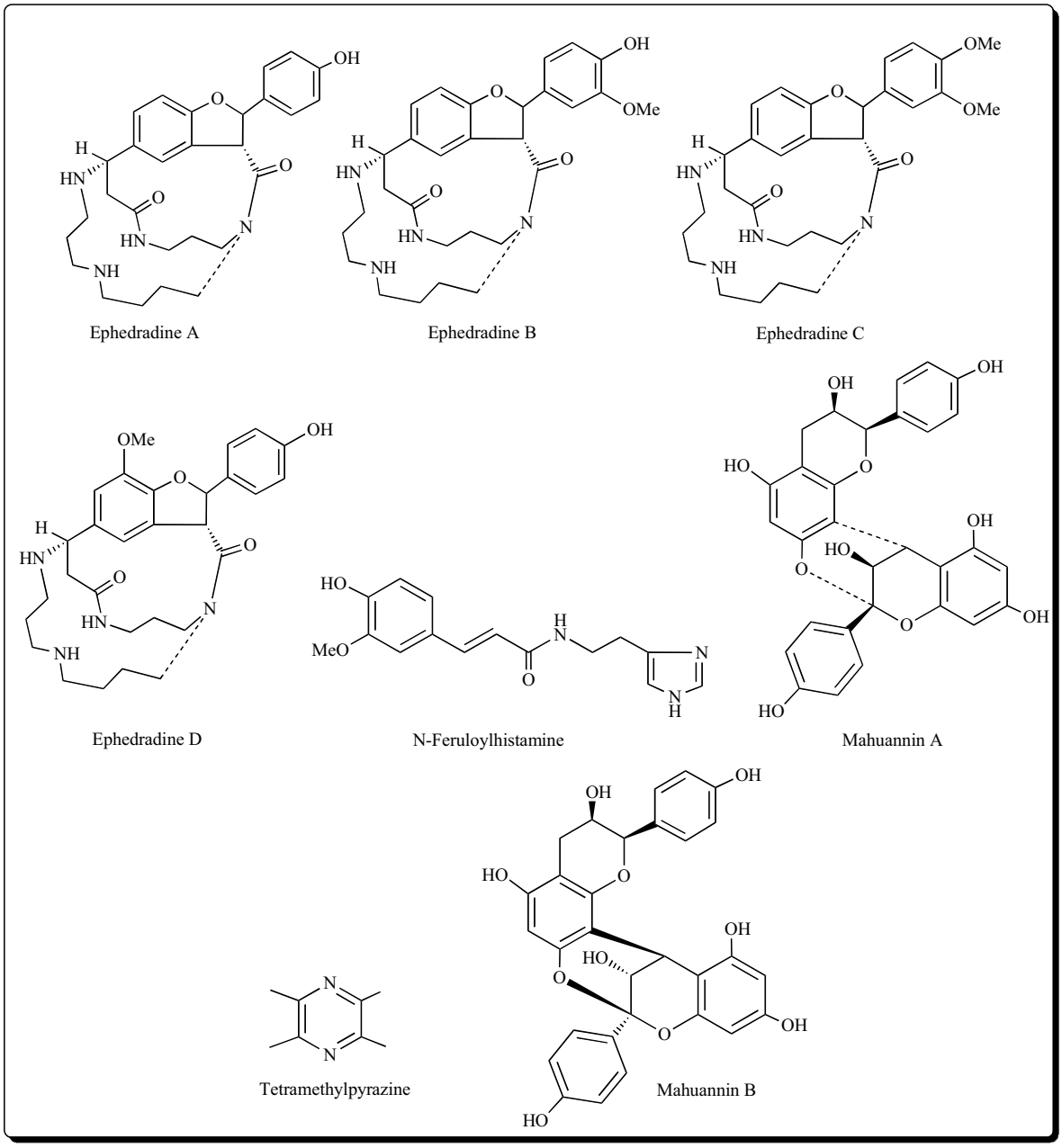
The activity-guided fractionation of the hydroalcoholic extract of trunk bark of *Cedrelopsis grevei* (Meliaceae) led to the isolation of five coumarins, as a part of the constituents responsible for the vasorelaxing activity observed for the crude extract [24].

Found in the fruit of *Cnidium monnieri* (L.) All four coumarins exhibited relaxing effect in PE_precontracted corpus cavernosum [25].

Found in *Olea europaea* leaves showed antihypertensive and negative inotropic properties [26].

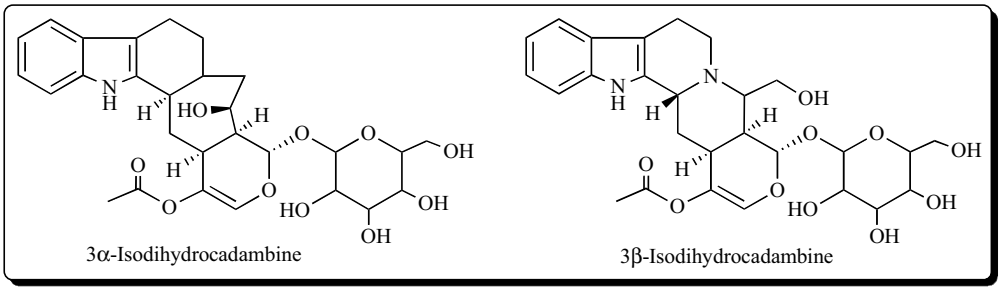
FLAVONOIDS

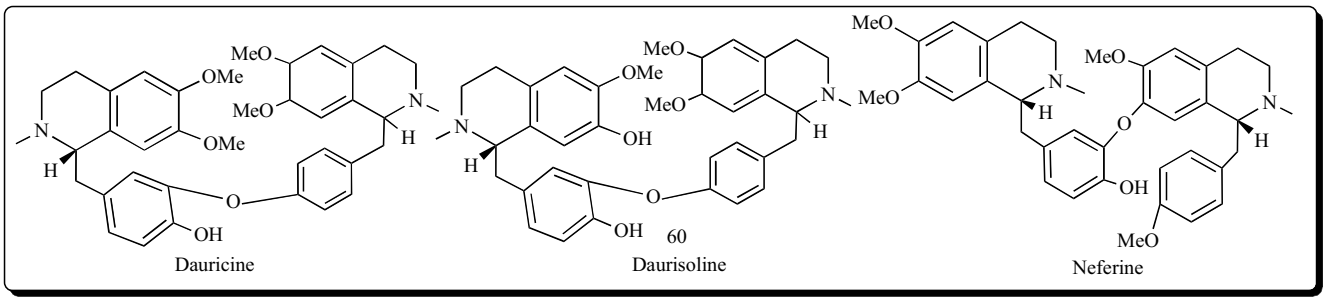
Properties of chrysin have been widely investigated by several authors. Chrysin relaxed the contractions induced by noradrenaline in isolated endothelium-intact rat aortic rings (IC_{50} = 16 ± 4 μM). Endothelium removal and N^G-nitro$_L$-arginine methyl ester inhibited this relaxant effect. Chrysin potentiated the relaxation to acetylcholine under control conditions or after incubation with the superoxide anion genera-



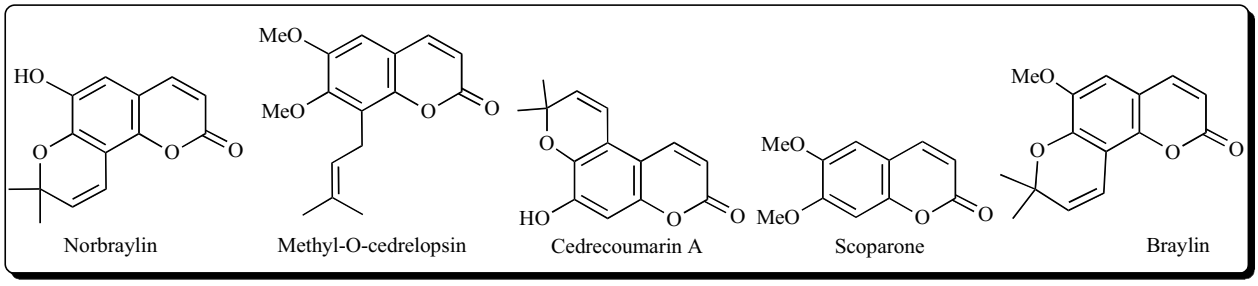
tor hypoxanthine/xanthine oxidase [27]. In another report, the antiaggregatory effect of 3-methylquercetin was only important for a concentration of 1 x 10^{-4} g/ml (3 x 10^{-4}M), which proved to be toxic for isolated cells. Inhibited cyclo-oxygenase but their activity was lower in comparison with that of indomethacin. 3-Methylquercetin had a positive chronotropic effect on the guinea pig right atrium in a concentration which was 4 times lower than the 50 % cytotoxic dose [28].

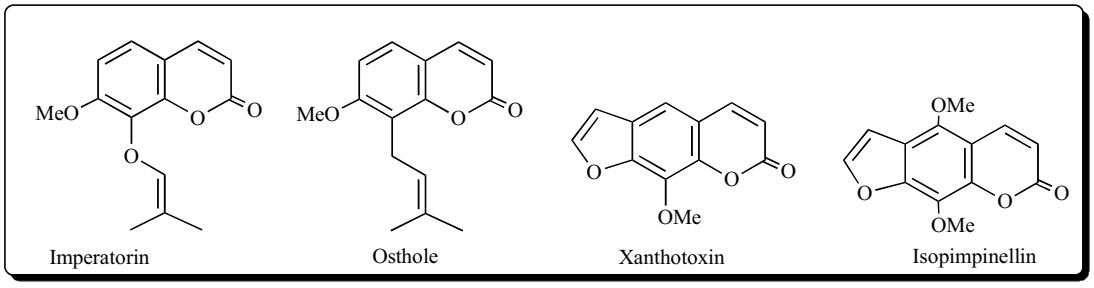
Recent experiment has shown that these compounds found in *Citrus limonum* (Rutaceae) possess antihypertensive activity [6].

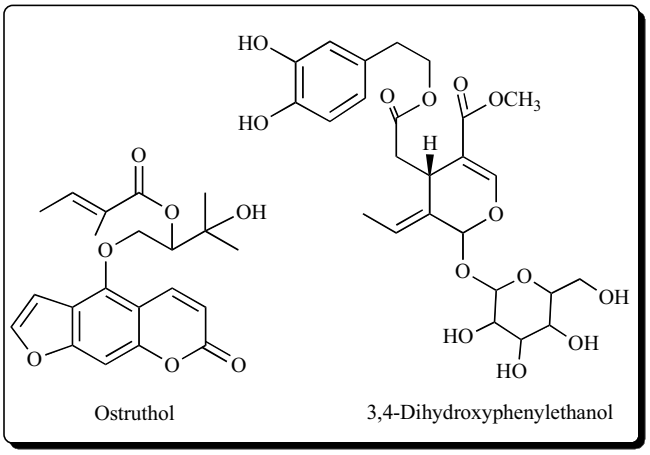




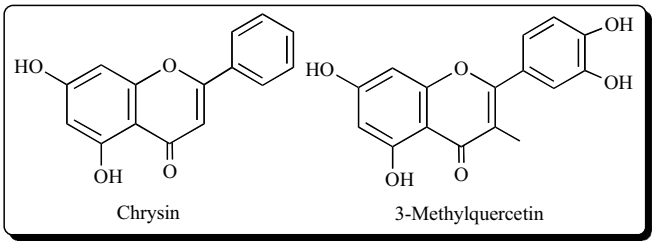
Naringenin, isolated previously from *Satureja obovata* Lag. relaxed in a concentration dependent manner the noradrenaline and KCl induced contractions. The vasodilator effect of naringenin in rat thoracic aorta could be mainly related to the inhibition of PKC [29]. In another report, ternatin, a tetramethoxy flavone isolated from *Egletes viscosa* Less, showed antithrombotic activity *in vitro* platelet aggregation indeed by ADP and *in vivo* mouse model of tail thrombosis induced by kappa-carrageenan (KC), ADP-induced platelet aggegation was inhibited by ternatin in a concentration-dependent manner with an IC_{50} of 390 μM, It also provided marked protection of mice from thrombotic challenge with KC, Tail thrombosis was totally prevented in mice that received ternatin prophylactically (1 h prior to KC injection) [30].

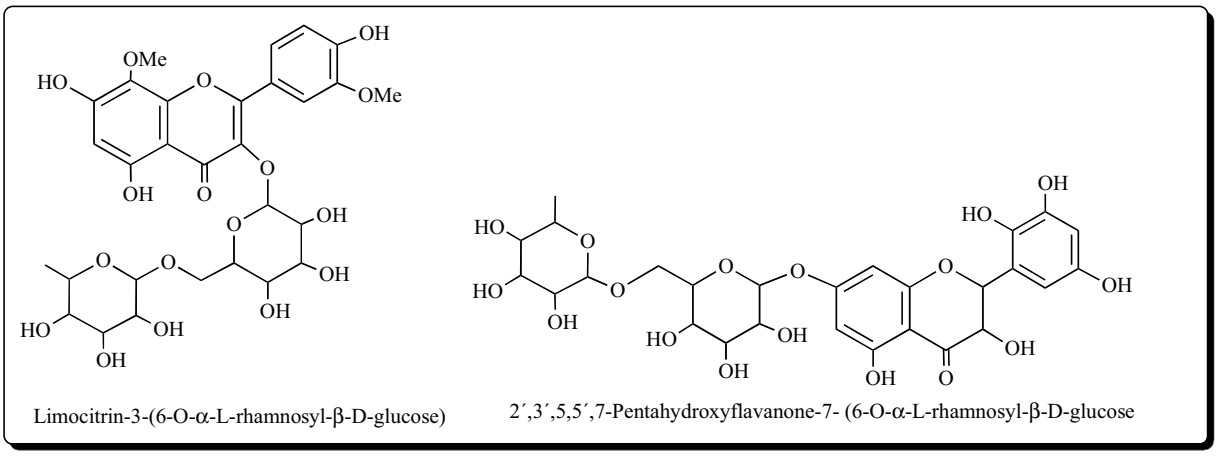




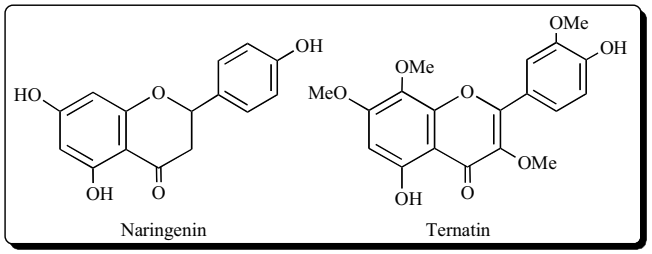


Ibarra and coworkers [31], demonstrated the isorhamnetin and quercetin produced endothelium-independent vasodilator effects in rat aorta, rat mesenteric arteries, rat portal vein and porcine coronary arteries. The effects of the two flavonoids were similar in arteries stimulated by noradrenaline. KCl, U46619 or phorbol esters but the two flavonoids were more potent in the coronary arteries than in the aorta. At high concentrations, they also induced a positive inotropic effect in isolated rat atria. Therefore, at least part of the *in vivo* effects of quercetin may result from its conversion to

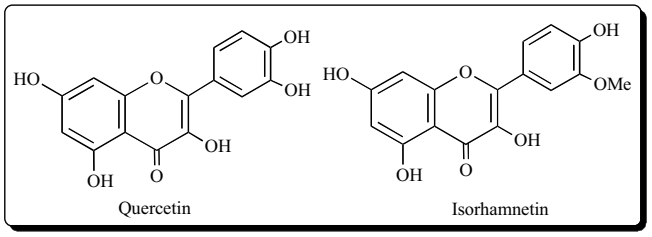




isorhamnetin which is the main metabolite of quercetin found in plasma. The arterial, venous and coronary vasodilator effects may contribute to the protective effects of flavonoids in ischaemic heart disease observed in epidemiological studies.



Is well known that flavonoids are potent vasodilators, the presence of these compounds in the aqueous extract of



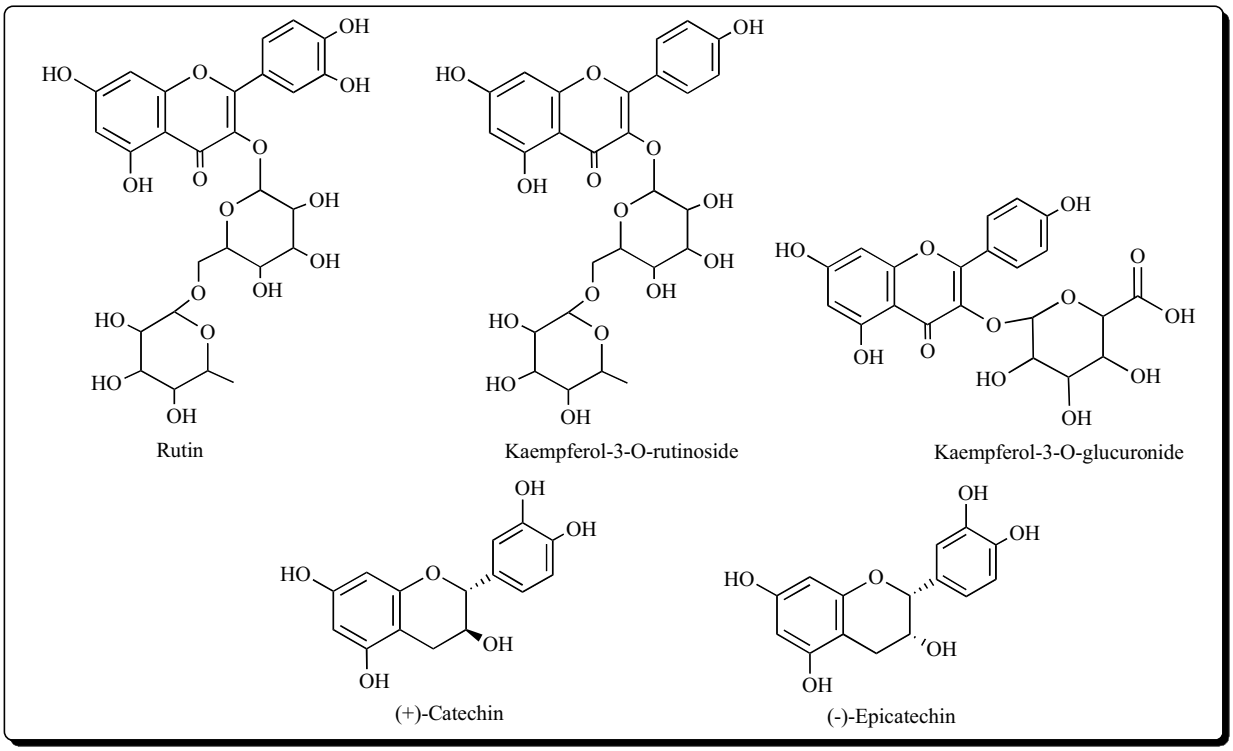
Alpinia zerumbet (Zingeberaceae) may play an important role in its antihypertensive action. Rutin has been reported to induce smooth muscle relaxation in various *in vitro* preparations. In addition, this flavonoid is a non-competitive inhibitor of angiotensin II and prostaglandin E2, interferes with arachidonic acid metabolism, and inhibits cAMP-phosphodiesterase [32]. Therefore, quercetin, the aglycon of rutin, is released by glycosidases produced by resident microflora of the bowel. These substances inhibits the contractions in rat aortic strips induced by noradrenaline, KCl, Ca^{2+} and phorbol 12-myristate, 13-acetate in a concentration-dependent manner [33].

So reported that ethanol extract of the roots of *Angelica keiskei* inhibited phenylephrine-induced vasoconstriction in rat aortic rings. These active substances inhibited phenylephrine-induced vasoconstriction at the concentrations of 10-100 μg/ml. It was found that xanthoangelol, 4-hydroxyderricin, and xanthoangelols E and F inhibited the phenylephrine-induced vasoconstriction through endothelium-dependent endothelium-derived relaxing factor (EDRF) production and/or nitric oxide (NO) production. In addition, xanthoangelol B inhibited the phenylephrine-induced vasoconstriction most strongly, and it inhibited the phenylephrine-induced vasoconstriction in the presence or absence of endothelium and in the presence or absence of N^G-monomethyl-$_L$-arginine (L-NMMA) (an NO synthetase inhibitor) [34]. Recent experiment have shown that xanthoangelol decreases serum LDL levels, in the liver, Dietary xanthoangelol results in a reduction of serum LDL levels and decreases in total cholesterol and triglyceride contents in the liver of SHRSP. These beneficial effects are more effective following consumption of diet containing 0.10% xanthoangelol [35].

In other study the isoflavone genistein, daidzein and 4-Hydroxyderricin were isolated from ethyl acetate extract of *Angelica keiskei* showed protective effect against hypertension, *via* the mitigation of oxidative stress and prevention of nitric oxide (NO, a potent vasodilator) reduction, in spontaneously hypertensive rats (SHR) The isoflavone group also experienced a significant decrease in oxidative DNA damage in leukocytes, using comet assay. DNA damage correlated positively with incremental BP during the study, and systolic BP at the end of the study ($p<0.01$). The results indicate that soy isoflavone has an antihypertensive effect, possibly through the amelioration of oxidative stress, and the augmentation of NO production, in SHR [36]. In another report 4-hydroxyderricin elevated serum high-density lipoprotein levels and reduced liver triglyceride content in stroke-prone spontaneously hypertensive rats (SHRSP). 4-Hydroxyderricin, a characteristic chalcone isolated from the yellow liquid of stems, produces suppression of the elevation of systolic blood pressure, reduction of serum levels and a decrease in hepatic triglyceride content in SHRSP [37].

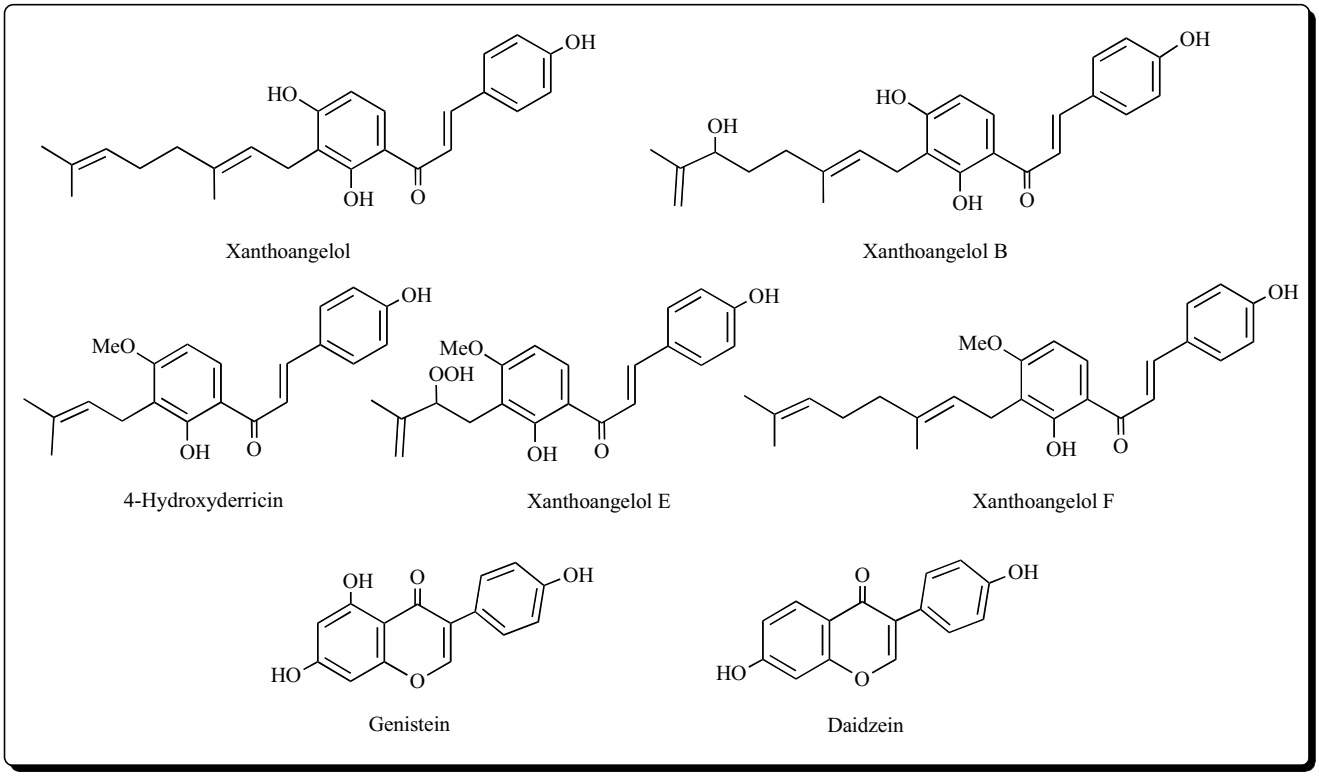
Several studies have indicated the ability of phenolic compounds to protect the cardiovascular system. The total amount of these compounds is 1-3 g/l in red wines and 0.2 g/l in whites. Malvidin 3-glucoside and procyanidin B1 may be responsible for the reduced incidence of coronary heart disease in people who regularly consume wine [38].

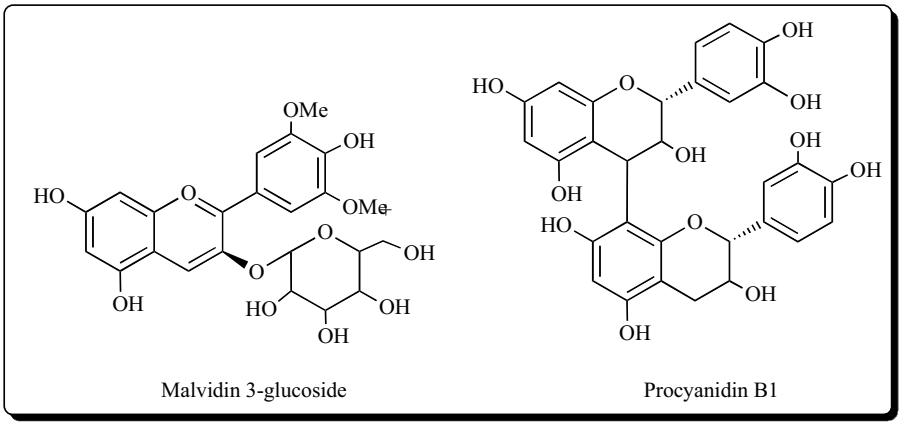
These flavonoids were found in *Morus alba* (Moraceae). Showed antihypertensive activity [6].



MONOTERPENOIDS, DITERPENOIDS AND SESQUITERPENOIDS

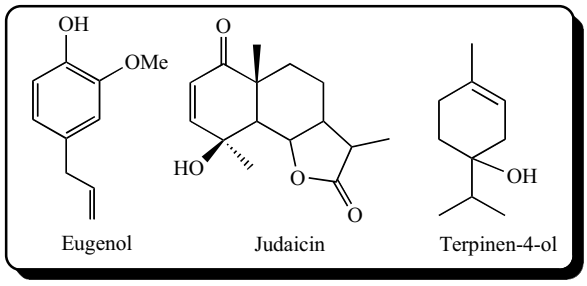
The effect of the cardiovascular effects of intravenous (i.v.) treatment with the essential oil of *Ocimum gratissimum* (Lamiaceae), and its main constituent, eugenol has been studied in the experimental model of deoxycorticosterone acetate (DOCA-salt)-hypertensive rats. In both conscious DOCA-salt hypertensive rats and their uninephrectomized controls, i.v. bolus injections of *O. gratissimum* (1-20 mg/kg) or eugenol (1-10 mg/kg) induced dose-dependent hypotension and bradycardia [39]. In another study judaicin found in *Artemisia judaica* L. (Compositae), caused a pro-



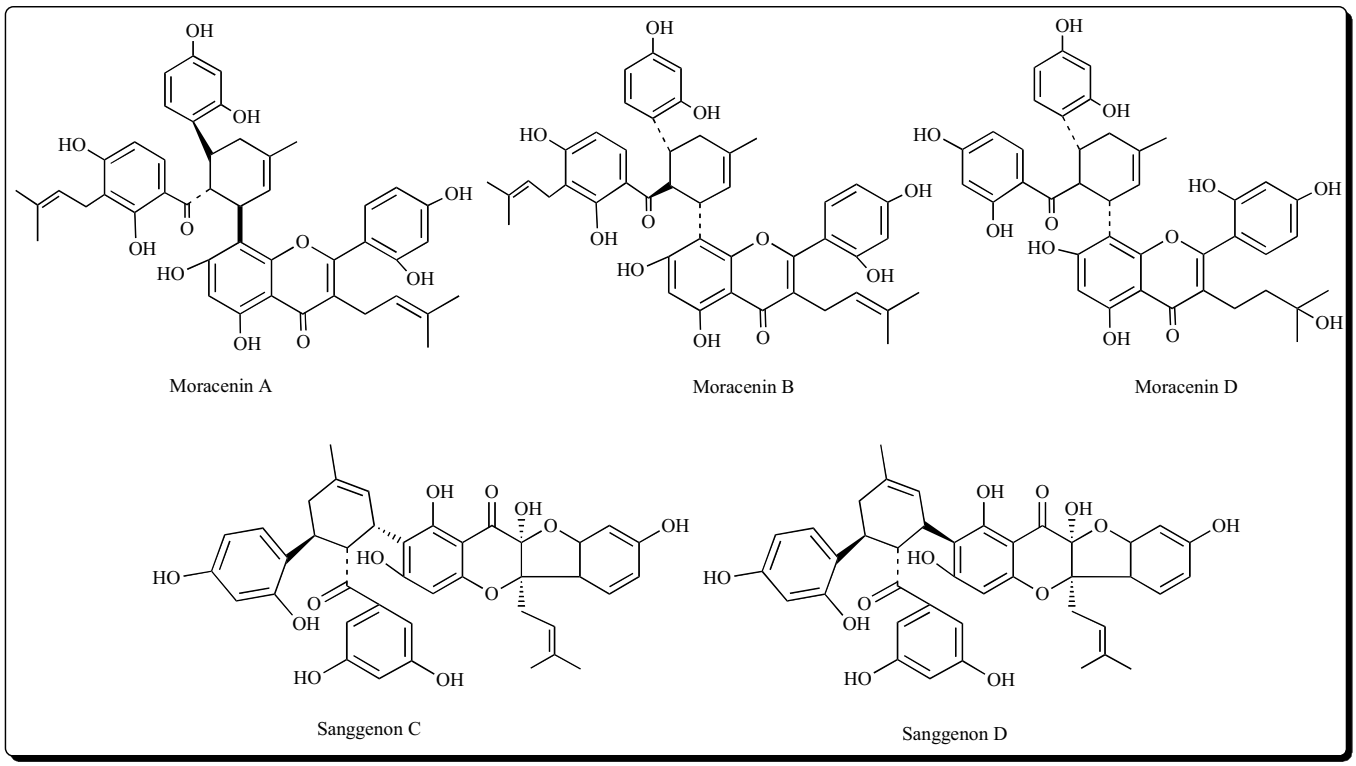


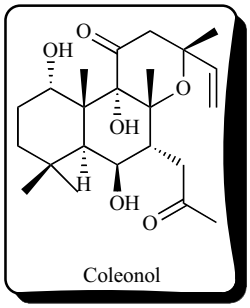
longation in the P-R interval and enforcement of the cardiac contractility [40]. In addition, terpinen-4-ol isolated from *Alpinia zerumbet* (Zingeberaceae) in the experimental model of (DOCA)-salt hypertensive rat and uninephrectomized, normotensive rats, i.v. bolus injections (1-10 mg/kg) decreased mean aortic pressure in a dose-related manner [32].

Coleonol, a diterpene, isolated from *Coleus forskohlii* showed predominant effect is to lower the blood pressure of anaesthetised cat and rat as well as of the spontaneously hypertensive rat due to relaxation of the vascular smooth muscle. In small doses it has a positive inotropic effect on isolated rabbit heart as well as on cat heart *in vivo*. So reported that coleonol also exhibits nonspecific spasmolytic activity on smooth muscle of the gastrointestinal tract in various species but not on bronchial musculature of guinea pig. Large doses of colecnol have a depressant action on the central nervous system [41]. Moreover, forskolin exhibits potent positive inotropic and hypotensive properties. Also lowers the intraocular pressure in rabbits, monkeys and humans activity.

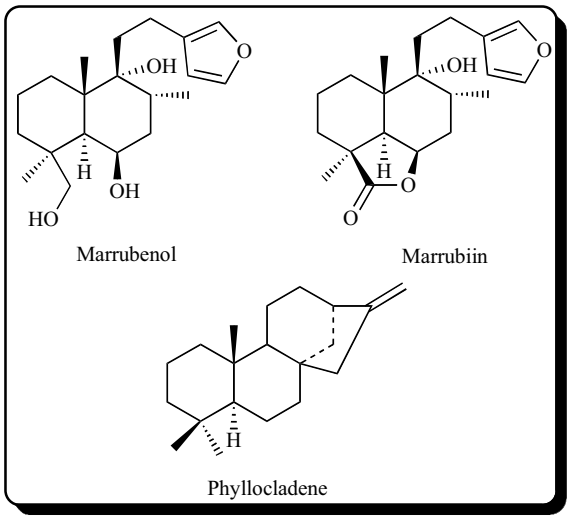


Recent experiment have shown that crude extracts of the aerial parts of *Marrubium vulgare* (Lamiaceae) show a potent *in vitro* inhibition of KCl-induced contraction of rat



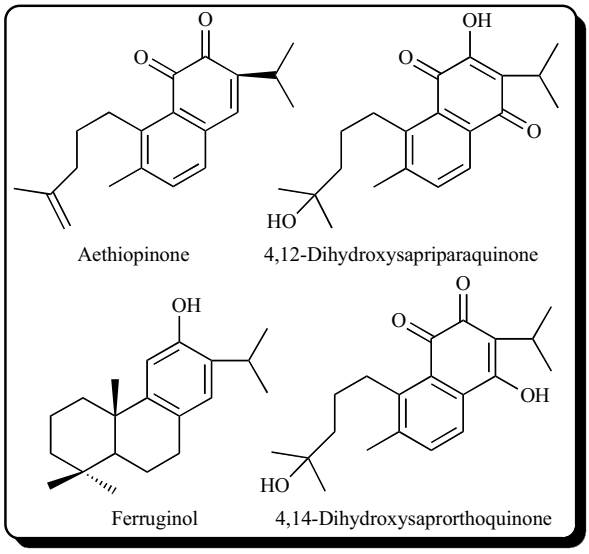


aorta. The furanic labdane diterpenes marrubenol and marrubiin isolated of the chloroform extract of *M. vulgare* showed vasorelaxant activity [42]. Phyllocladene found in the leaf of



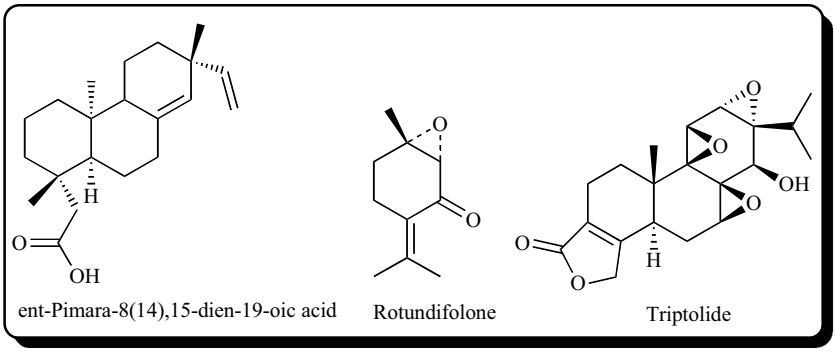
Dysoxylum lenticellare (Meliaceae) is a very cardiodepressant agent. Several studies have indicated the ability of phyllocladene ($3X10^{-6}$ M) to depress the rate of the rat isolated spontaneously-beating right atria. At 1ower concentrations of 10^{-7}M, it induced positive chronotropic effect [43]. Other studies show the negative chronotropic effect induced by phyllocladene, was modified by prior administration of atropine, which reduced or abolished the negative chronotropic effects of acetylcholine. This suggests that this effect is mediated through the cholinergic mechanism [44].

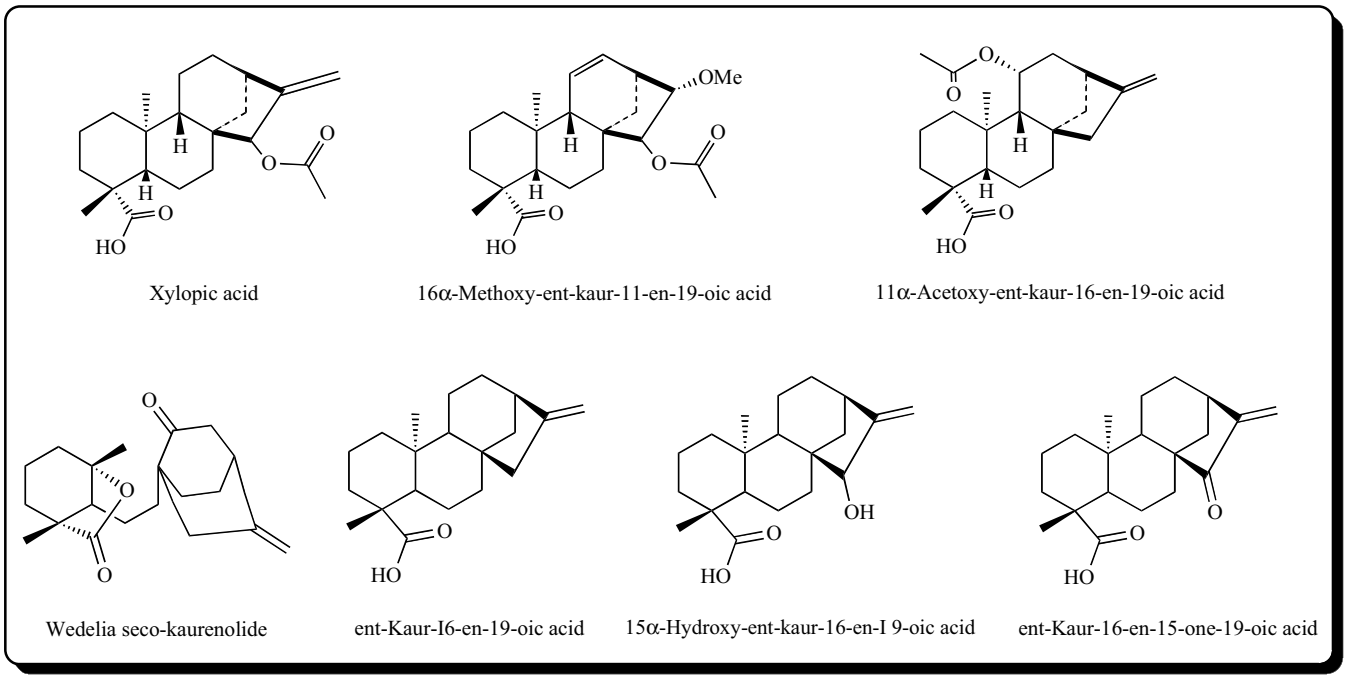
ent-Pimara-8(14),15-dien-19-oic acid was isolated from *Viguiera arenaria* (Asteraceae;Heliantheae) inhibited rat carotid rings contraction induced by phenylephrine (10^{-8} mol/1) or potassium chloride (45 mmol/1) at concentration ranging from 5 to 20 μg/m1. This inhibitory effect was not reversible after the removal of this compound from the medium bath. Rotundifolone, the major constituent (63.5 %) of the essential oil of *Mentha x vi1losa* Hudson (Lamiaceae) induced a significant and dose-dependent hypotension and bradycardia in non-anaesthetized normotensive rats. Also rotundifolone**,** markedly lowers arterial pressure and heart rate in non-anaesthetized animals. In addition, the hypotensive action of rotundifolone can be a consequence of an in heart rate and peripheral vascular resistance, probably due to a non-selective muscarinic receptor stimulation [45]. Hu and coworkers [46] demonstrated that the triptolide, the major component of the diterpenoids of the Chinese herb *Tripterygium wilfordii* Hook f. (Celastraceae), inhibited vascular endothelial growth factor expression and secretion in endothelial cells treated by 12-O-tetradecanoylphorbol 13-acetate dose-dependent manner. This effect may be one of the mechanisms underlying the therapeutic effects of triptolide on rheumatoid arthritis.



From the roots of *Salvia eliophora* (Lamiaceae), were isolated 4,14-dihydroxysaprorthoquinone, aethiopinone, ferruginol, 4,12-dihydroxysapriparaquinone and 6,7 dehydroroyleanone, has been that it possess effects on blood pressure, it is probably due to the vasorelaxation activity [47].

All these diterpene kaurenoids were isolated from *Alepidea amatymbica* (Apiaceae) and *Xylopia aethiopica*

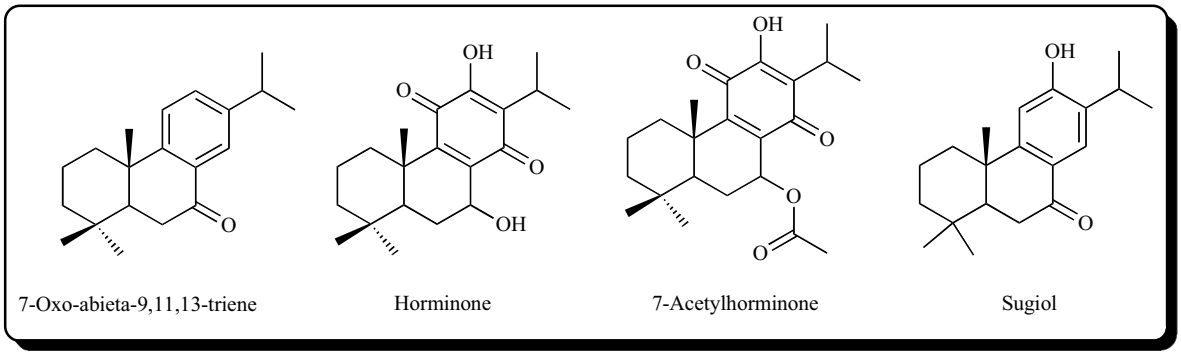




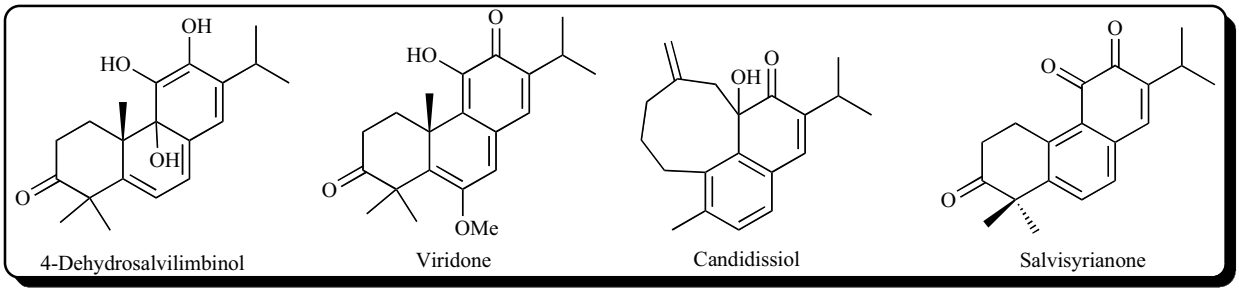
(annonaceae), have significant systemic hypotensive and coronary vasodilatory effect accompanied with bradycardia. The effects were attributed to calcium antagonistic mechanism. The diuretic and natriuretic activities found were similar to the chlorothiazide, these findings suggest inhibition of Na^+ and K^+ reabsorption in the early portion of the distal tubule [48].

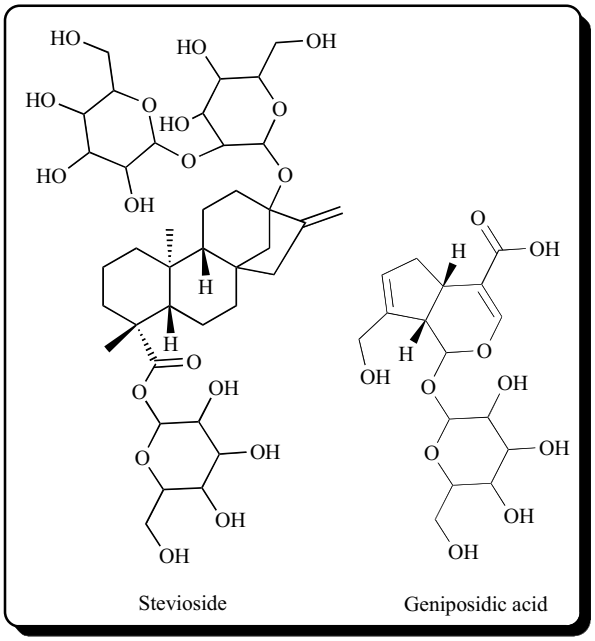
These diterpenoids, were isolated from the roots of *Salvia amplexicaulis* lm. (Lamiaceae). All of the compounds strongly showed a vasodepressor effect on rats [49].

Several studies have indicated the ability antihypertensive of these diterpenes isolated from *Salvia syriaca*. (Lamiaceae) on rats [50].



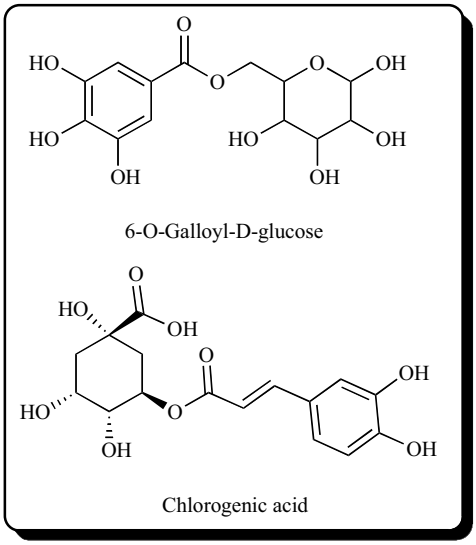
Stevioside, was found in *Stevia rebaudiana* (Compositae), produced a significant increase in myocardial sensitivity to verapamil, but no toxic effect was observed in any of the cases. A similar conclusion also holds for the interaction with MKHNa (bile acid), whereas ME (monoketocholic acid methyl ester) caused an increase in the toxicity of verapamil [48]. Other studies show that geniposidic acid was isolated





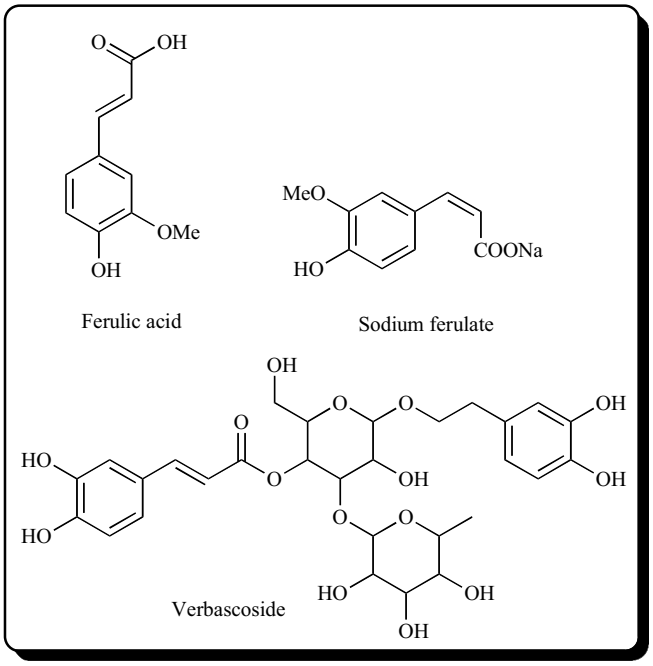
from the methanol extract of *Eremophila longifolia* (Myrtaceae) leaves, mediated an inhibitory effect with significant negative chronotropism, negative inotropism and CPR [51].

PHENOLIC, LIGNANS, NEOLIGNANS AND TANNINS



Phenolic glycoside (6-O-galloyl-D-glucose) contained in the leaves of *Sapium sebiferum* (Euphorbiaceae) showed hypotensive action appears to be produced by an inhibition of noradrenaline release and/or a direct vasodilatation [52]. Moreover, chlorogenic acid in green coffee bean extract reduced blood pressure in spontaneously hypertensive rats and humans. Treatment with both compounds is effective in decreasing blood pressure and safe for patients with mild hypertension [53].

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phenolic compound contained in rice bran and other plants. After oral administration of ferulic acid (1 to 100 mg/kg) to

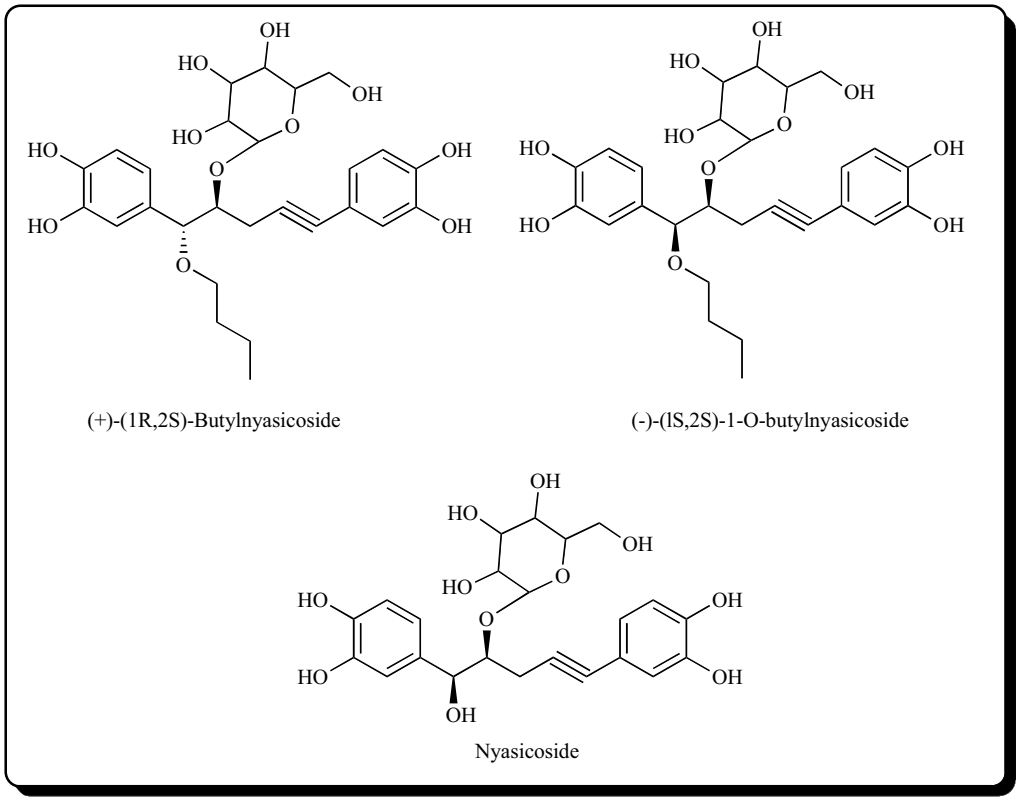


spontaneously hypertensive rats SHR, systolic blood pressure (SBP) significantly decreased in a dose-dependent manner. The hypotensive effect of ferulic acid in SHR is associated with NO-mediated vasodilation [54]. In another study, was observed that the sodium ferulate or 3-methoxy-4-hydroxy-cinamate sodium is the active principle from *Angelica sinensis* (Umbelliferae), and *Cimicifuga heracleifolia* (Ranunculaceae) and other plants. It has been used in traditional Chinese medicine and is approved by State Drugs Administration of China as a drug for treatment of cardiovascular and cerebrovascular diseases. Several studies have indicated the ability of sodium ferulate as antithrombotic, platelet aggregation inhibitory and antioxidant activities in animals and humans [55]. Several studies have been performed with *Eremophila* species (Myoporaceae) considered important in the pharmacopoeia of the Australian Aboriginal people. Continuing with the study the verbascoside, isolated from the methanol and water extracts of *Eremophila alternifolia* leaves, mediated significant increases in chronotropism, inotropism and coronary perfusion rate (CPR) in the Langendorff rat heart. [56].

Found in *Curculigo capitulate* (Amaryllidaceae) possessed potent activity against ouabain-induced arrhythmia in the heart preparations of guinea pig [57].

Found in *Cuscuta japonica* (Convolvulaceae). These compounds inhibited the angiotensin I converting enzyme activity in a dose-dependent manner. Compounds showed the IC_{50} values of 596 μM for 3,5-di-*O*-caffeoylquinic acid, 483 μM for methyl-3,5-Di-*O*-caffeoylquinate, 534 μM for3,4-Di-*O*-caffeoylquinic acid, and finally methyl 3,4-Di-*O*-caffeoylquinate with 460 μM. The presence of these active components may be responsible, at least in part, for the antihypertensive action of traditional crude drug "Cuscuta Semen" [58].

Caffeoylquinic acids and flavonoids are two major groups of constituents of artichoke leaf extract. Interestingly,

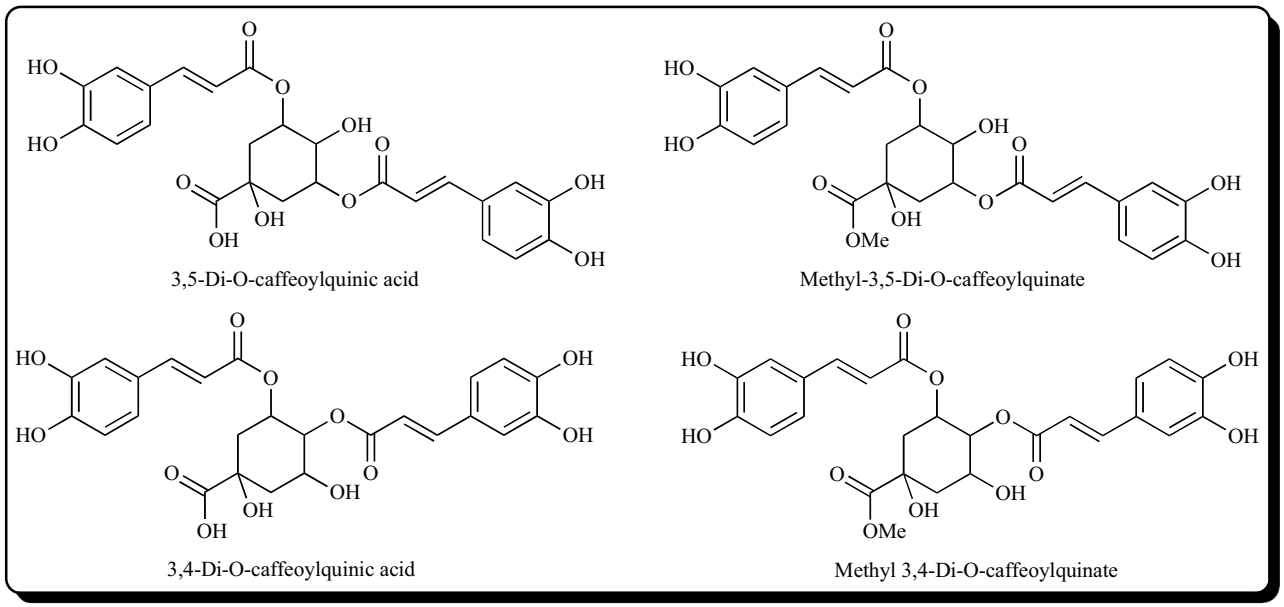


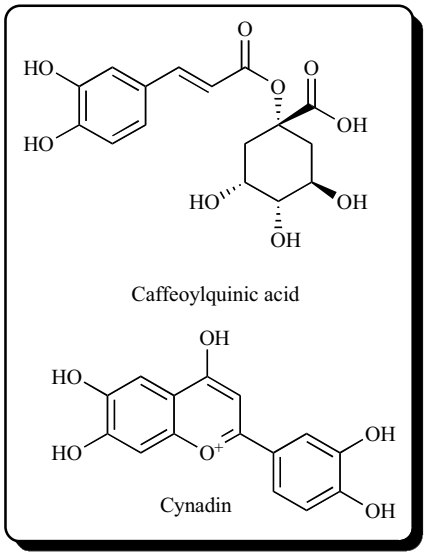
the flavonoids luteolin and cynaroside increased endothelial nitric-oxide synthase (eNOS) promoter activity and eNOS mRNA (measured by an RNase protection assay) expression, whereas the caffeoylquinic acids cynarin and chlorogenic acid were without effect. Thus, in addition to the lipid-lowering and antioxidant properties of artichoke, an increase in eNOS gene transcription may also contribute to its beneficial cardiovascular profile. Artichoke flavonoids are likely to represent the active ingredients mediating eNOS up-regulation [59].

D-003 is a natural mixture of higher primary saturated aliphatic acids purified from sugar cane wax, whose main component is octacosanoic acid followed by triacontanoic, dotriacontanoic, and tetratriacontanoic acids. D-003 inhibits platelet aggregation and arterial thrombosis experimentally induced in a dose-dependent fashion [60].

TRITERPENES

Triterpenes, found in the stems of *Tinospora crispa* (Menispermeaceae). Cycloeucalenol slightly increased the right



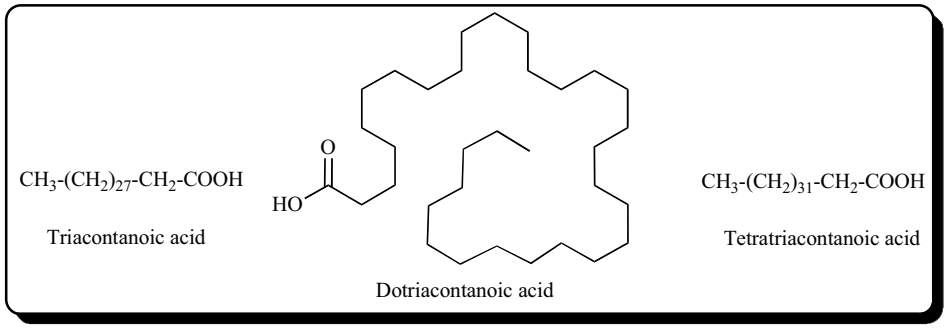


atrial force of contraction whereas it showed an initial reduction followed by sustained reduction of about 10% on the left atria of the rat *in vitro*. In addition, cycloeucalenone showed slight change from the control on the right and left atrial force. These results suggest that cycloeucalenol and cycloeucalenone produced mild cardiotonic effects [58]. Other studies show glycyrrhizinic acid found in *Glycyrrhiza glaba* (Fabaceae) is a substance that acts upon the adrenal cortex to produce sodium retention, expansion of the extracellular fluid volume, hypertension and a reduction of the plasma levels of renin and aldosterone [61].

Ilexolide A, extracted from the roots of *Ilex pubescells* (Fagaceae) exhibits cardiac activity. Vasodilation is cause by inhibiting Ca^{2+} influx which in turn affects the adrenergic receptors. Rest of triterpenoids together with β-sitosterol was isolated from the roots of *Salvia amplexicaulis* lam. (Lamiaceae). All compound possessing a vasodepressor effect on rats [62].

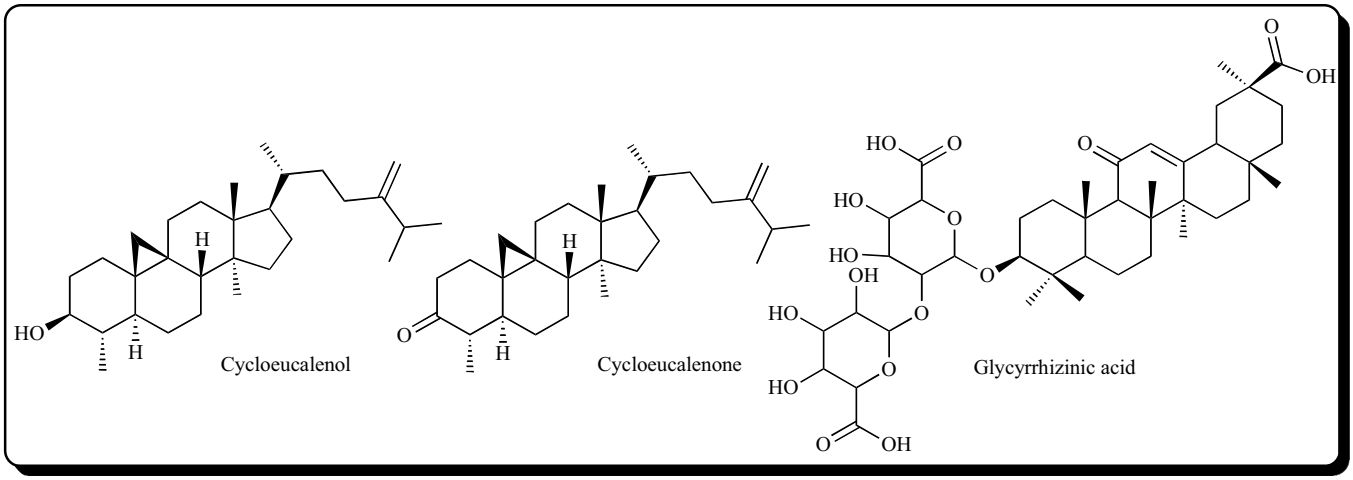
A steroidal saponin was isolated from the leaves of *Sansevieria cylilldrica* (Agavaceae). Its showed no haemolytic effects in the *in vitro* assays and demonstrated inhibition of the capillary permeability activity [63].

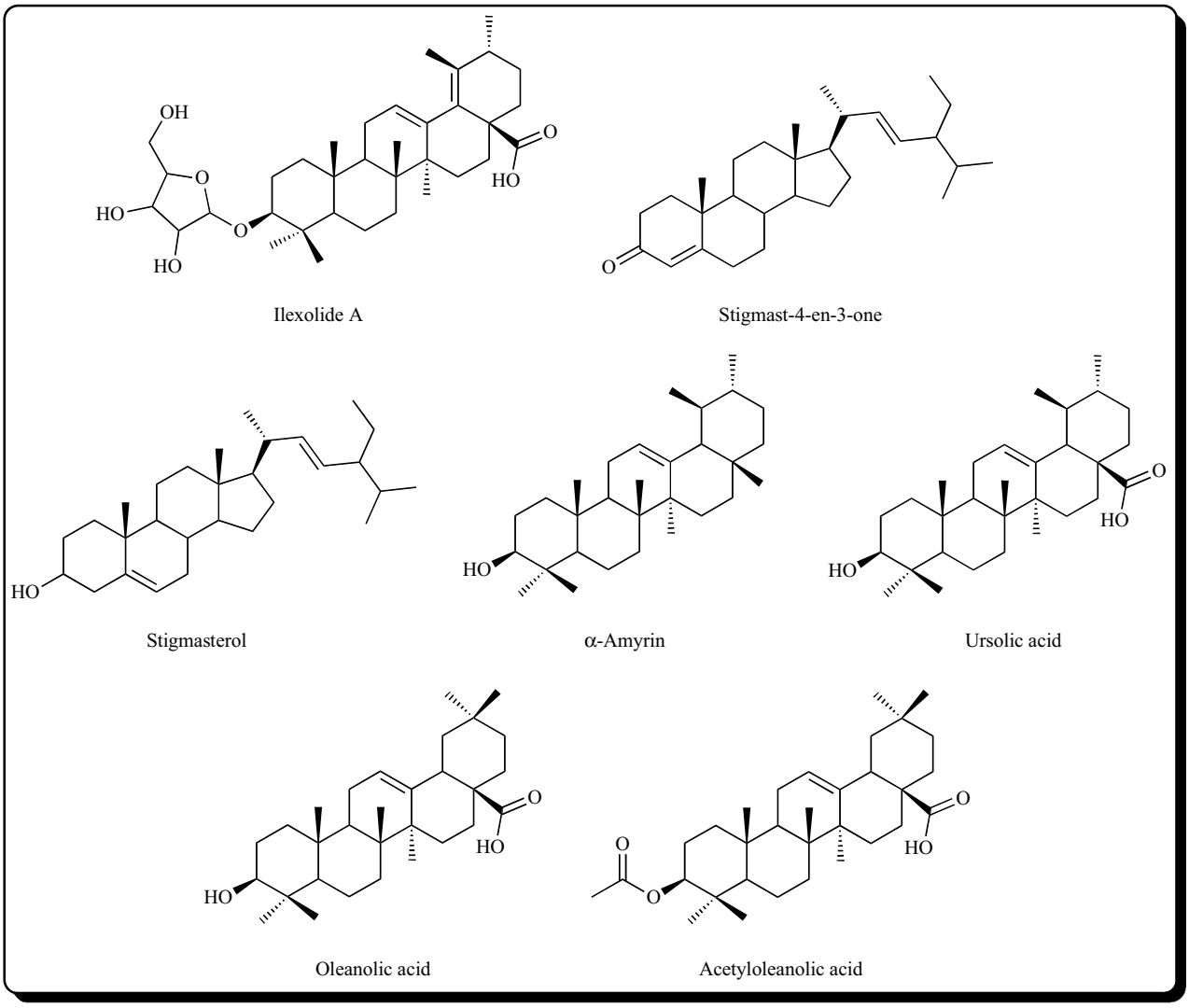
Saponins of *Panax quinquefolium* (Araliaceae), at a dose of 80 mg/kg i.v. inhibited the cardiac arrythmias induced by chloroform in mice, by barium chloride in rats and by ouabain in guinea pigs. Ginsenoside Rb_1 markedly increased the contractile force dose dependently. The activity of Na^+, K^+ - A T Pase was inhibited by ginsenosides R_{b1} and Re [64].



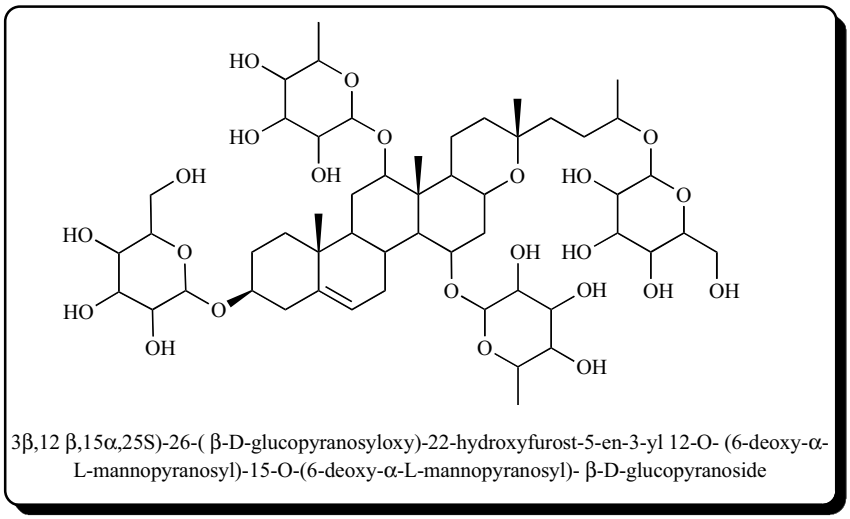
MISCELLANEOUS

Allicin, one of the active compounds produced by garlic (Liliaceae). Treatment with allicin (1, 2.5, or 10 μg), topically, lowered the IOP unilaterally in normal rabbits. Allicin (10 micrograms) reduced the intraocular pressure by 6 +/- 1 mmHg (n = 4) in normal rabbits at 2 hrs (maximum response) whereas no change occurred in sympathectomized

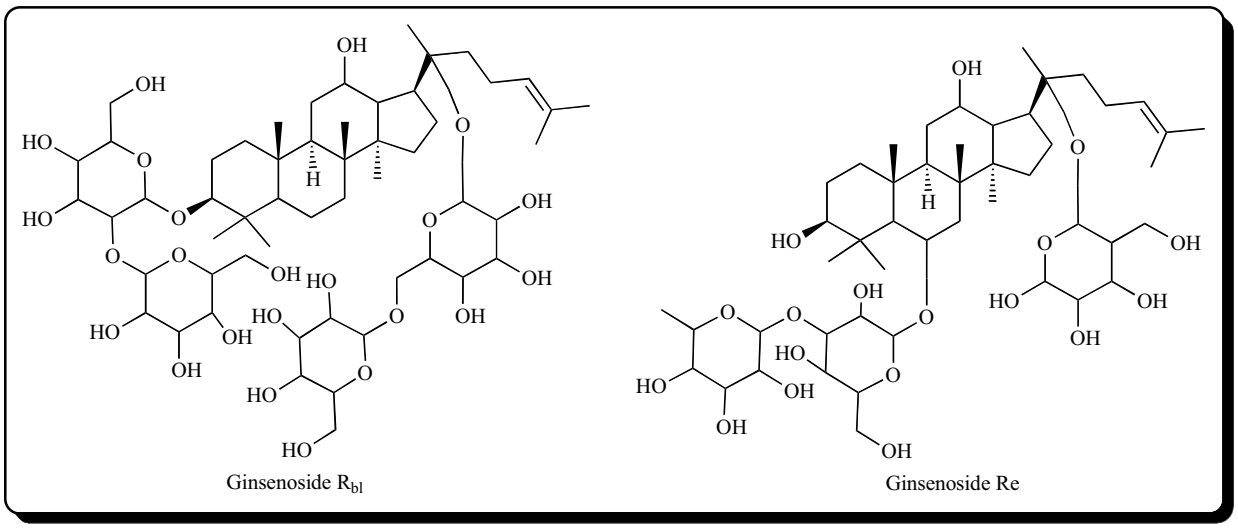




rabbit eyes. Moreover, allicin (0.01, 0.1, or 1 μM) caused 40, 40, or 52% inhibition, respectively, of 3H-NE overflow in response to electrical field stimulation. Also, allicin (1 μM) had no effect on basal cAMP level while it inhibited isoproterenol -stimulated accumulation in the rabbit iris-ciliary body by 40% and 23% in iris-ciliary body and nonpigmented epithelial cells, respectively [65].



3β,12 β,15α,25S)-26-(β-D-glucopyranosyloxy)-22-hydroxyfurost-5-en-3-yl 12-O- (6-deoxy-α-L-mannopyranosyl)-15-O-(6-deoxy-α-L-mannopyranosyl)- β-D-glucopyranoside

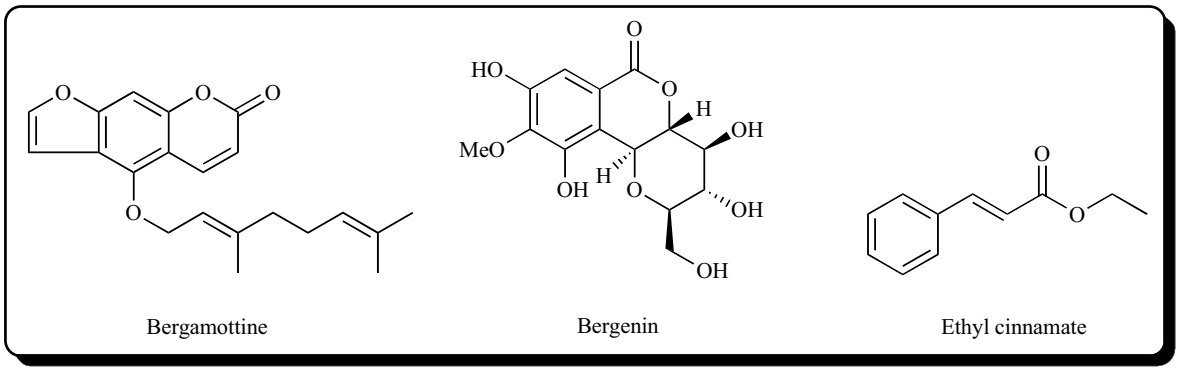


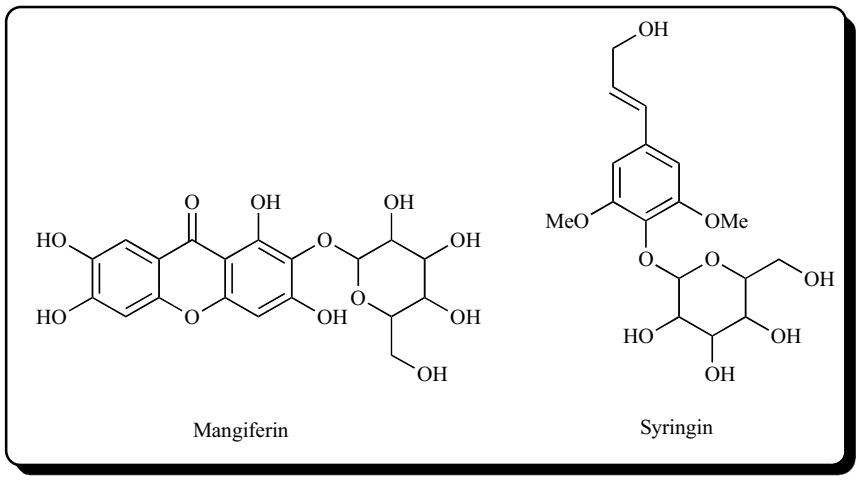
Bergarnottine, a furocoumarin isolated from Bergamot oil (*Citrus Bergamia* Risso, Labiadas) significantly decreased the typical electrocardiographic signs of coronary arterial spasm and the incidence of cardiac arrhythmias induced by pitressin in anaesthetized guinea-pigs. Bergamottine also increased the dose of ouabain required to cause ventricular premature beats, ventricular tachyarrhythmias and lethality. In addition, bergamottine further reversed ouabain-induced persistent ventricular tachycardia and restored sinus rhythm in the guinea-pig. On isolated rat heart, bergamot tine exerted a coronary dilator action and was able to reduce the hyperkinetic ventricular arrhythmias caused by post-ischaemic reperfusion [66]. In another report, bergenin was isolated from the aerial parts of *Fluggea virosa* (Euphorbiaceae). Showed anti-arrhythmic effects. At concentrations of 0.2 at 0.8 mg/kg, has been shown to possess distinct therapeutic effects on $BaCl_2$-induced arrhythmias in rats. At concentrations of 0.4 mg/kg and 0.8 mg/kg bergenin significantly countered arrhythmias induced by ligation and reperfusion of the coronary artery. At 0.8 mg/kg, elevated the atria fibrillation threshold in rabbits from 1.34 mV to 1.92 mV. These findings suggest that bergenin has good potential to treat cardiac arrhythmias [67]. In another report, the ethyl cinnamate was isolated from the rhizomes of *Kaempferia galanga*L. (Zingiberaceae), ethyl cinnamate [68]. Showed vasorelaxant effect on the rat aorta, the inhibitory effects may involve inhibition of Ca^{2+} influx into vascular cells and release of nitric oxide (NO) and prostacyclin from the endothelial cells. Thus: the vasorelaxant effect mediated through multiple pathways may explain the traditional use of the parent plant in treating hypertension.

GALACTOMANNANS

The crude galactomannans from *Phoenix dactylifera* (Leguminosae) and *Glycine max* (Leguminosae) exhibited anticoagulation activities comparable to that of standard heparin sodium. Also the anticoagulation activities of these galactomannan fractions isolated from the crude extract were low [69].

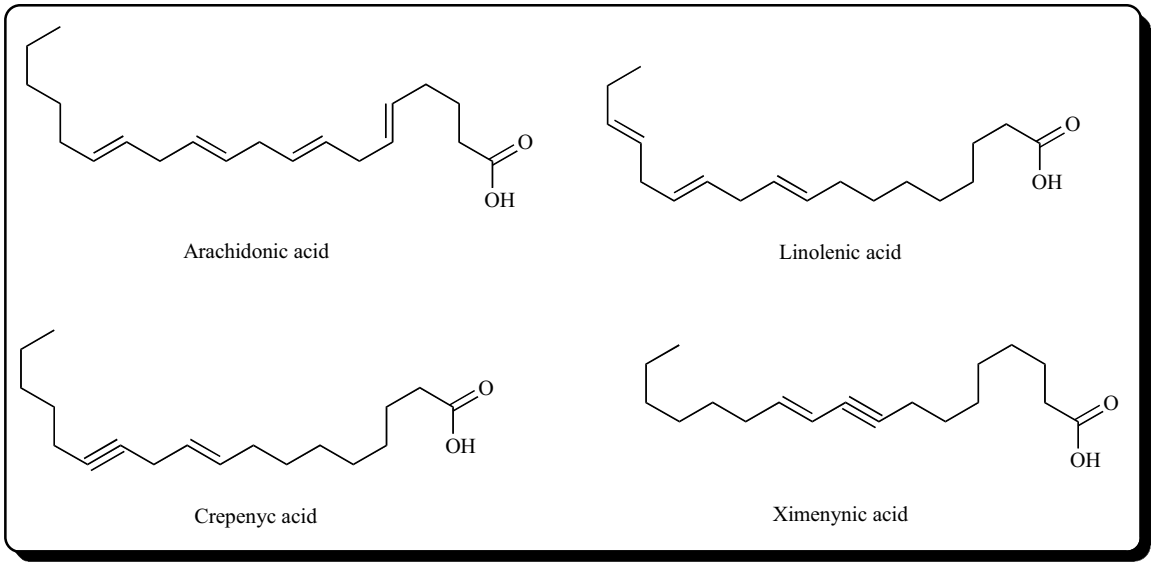
Mangiferin was isolated from *Mangiferia indica* L (Anacardiaceae). Treatment with mangiferin (0.025 mg/ml) inhibited the interleukin-1β (1ng/ml)-induced iNOS expression more in SHR than in WKY, and yclooxygenase-2 expression more in WKY than in SHR [70]. Several studies have indicated that the mangiferin (0.05 mg/ml) did not affect noradrenaline-induced contraction (Beltran *et al*., 2004). In another report syringin was isolated from the bark of *Syringa vulgaris* (Oleaceae). Continuing with the study, when the drug was introduced intravenously, it caused a dose dependent fall in systolic, diastolic and mean arterial blood pressure, whereas heart rate also decreased at a slightly higher dose. The hypotensive activity was not inhibited by





antihistamine or antimuscarinic agents. Syringin has no activity on the pressor effect induced by norepinephrine or carotid occlusion [71].

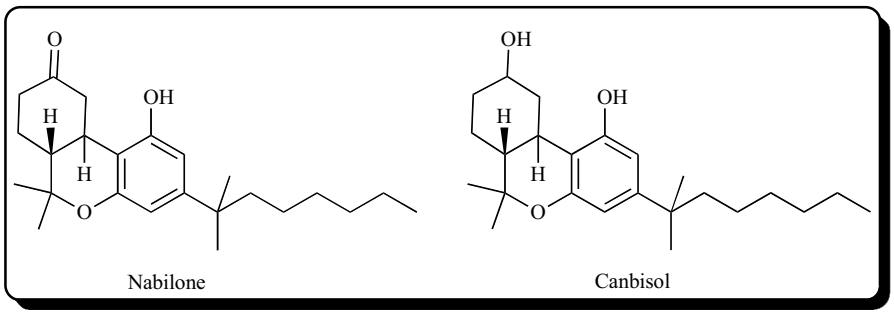
linked with this particular status were investigated. Ximenynic acid ethyl ester is endowed with an interesting vasokinetic activity [72].

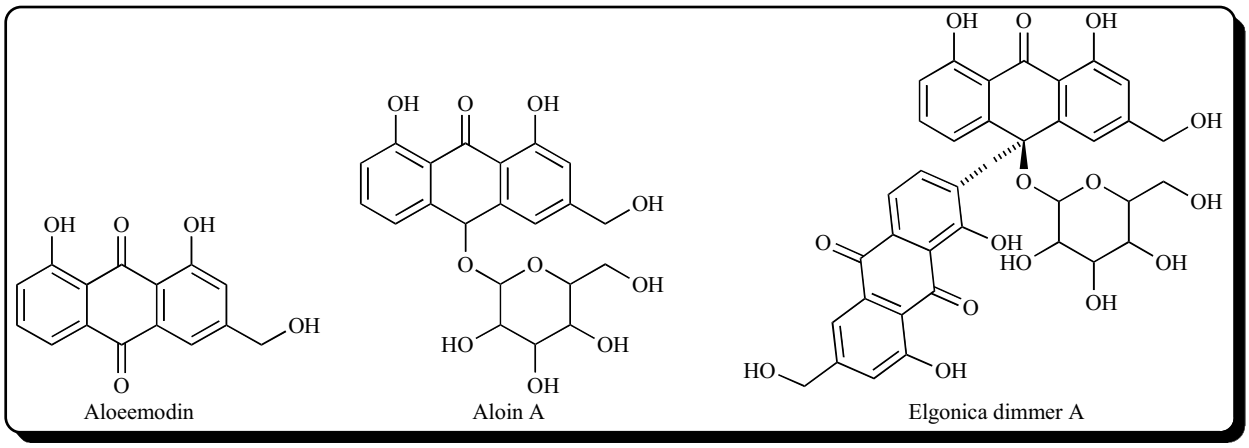


Ximenynic acid ethyl ester occurs widely in the seed lipids of many species of the *Santalaceae* and *Olacaceae*, showed efficacy on the microcirculatory misdistribution present in cellulites subjects. Since these subjects presented also signs of preclinical venous insufficiency, some parameters

Found in *Cannabis sativa* var. indica (Cannabinaceae). Recent experiment have shown that nabilone and canbisol showed antihypertensive activity [73].

Aloeemodin, aloin A, elgonica dimmer A from *Aloe barbadensis* (Liliaceae) showed hypotensive effects. Aloee-





modin has emerged as a potent hypotensive agent in current pharmacological investigations and caused 26%, 52%, and 79% falls in mean arterial blood pressure at the corresponding doses of 0.5, 1, and 3 mg/kg in rats [74].

Found in celery (*Apium graveolens,* Apiaceae). All compounds have been shown to possess hypotensive and vasorelaxant effects. Treatment with 3-n-Butylphthalide at doses of 2.0 and 4.0 mg/day for thirteen days produced a transient hypotensive effect [75]. In another study brazilein is a compound with a non-steroidal skeleton, obtained in a large amount from *Caesalpinia sappan* ethanol extracts. In isolated cardiac tissues, brazilein exhibited a positive inotropic action in a concentration-dependent manner with little effect on heart rate and coronary perfusion. Also brazilein, produced its positive inotropic effect through inhibiting Na^+, K^+-ATPase and could thus serve as a structural paradigm to develop new inotropic drugs [76].

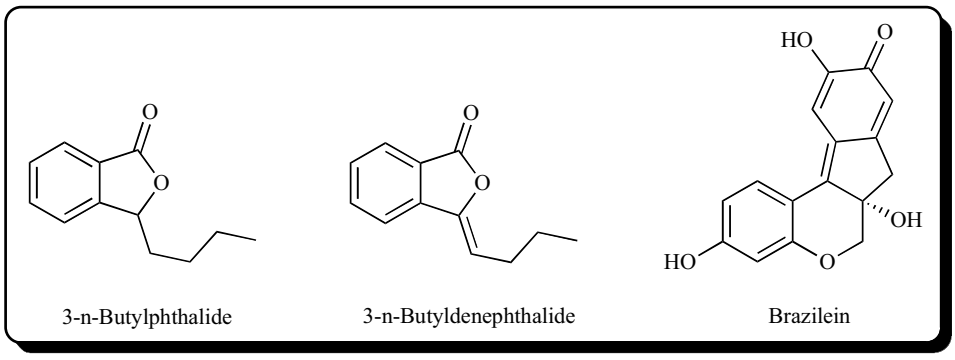
Found in *Morus bombycis* and *M. lhou* (Moraceae). Showed antihypertensive activity [73].

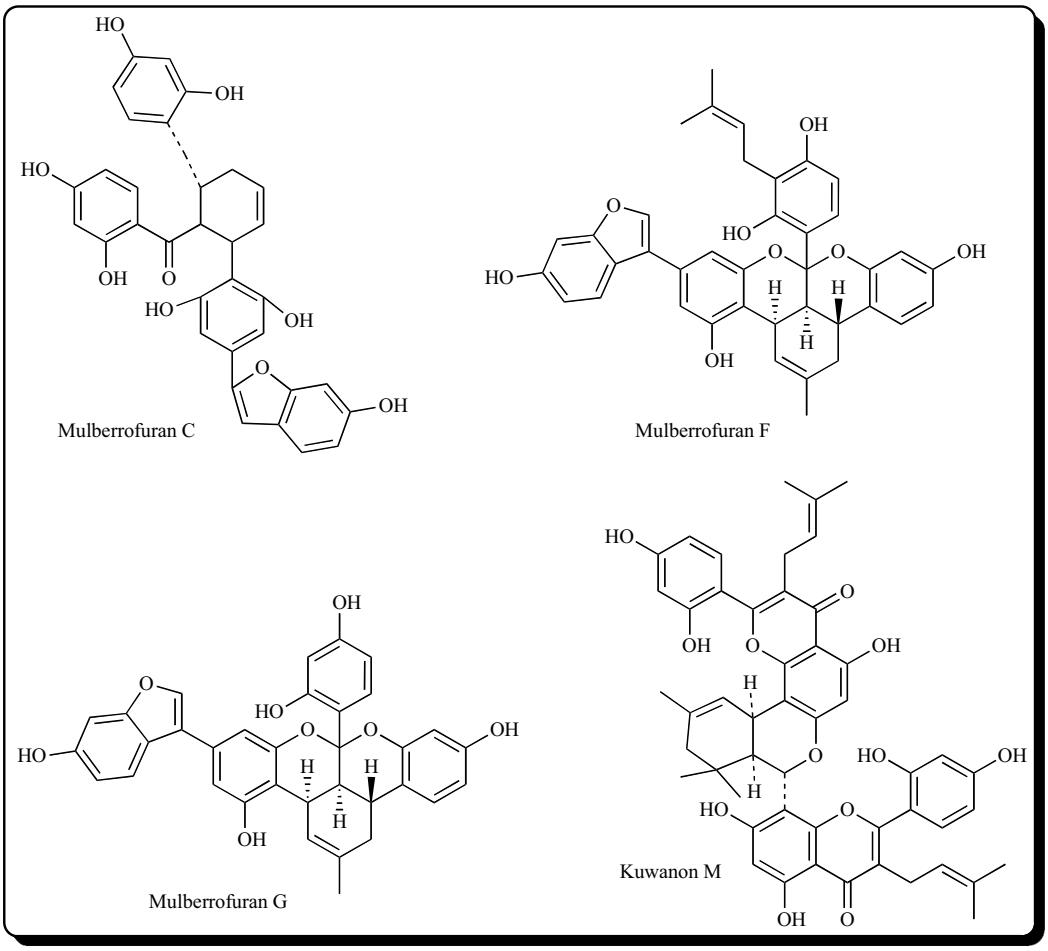
Found in the methanolic extract of *Tagetes patula* roots. Citric and malic acid and pyridine hydrochloride showed hypertensive activity. Citric acid and malic acid caused 71% and 43% fall in mean arterial blood pressure (MABP) of rats at the doses of 15 mg/kg and 30 mg/kg respectively while pyridine hydrochloride produced 34% rise in the MABP of rats at the dose of 30 mg/kg. (Saleem *et al*., 2004). Geniposide is one of the constituents of Gardenia fruit (*Gardenia jasminoides* Ellis, Rubiaceae), which has been used in traditional medicine. In an *in vivo* model, geniposide and genipin significantly ($P < 0.05$) prolonged the time required for thrombotic occlusion induced by photochemical reaction in the mouse femoral artery [77]. In an *in vitro* study, both geniposide and genipin inhibited collagen-induced, but did not inhibit arachidonate-induced, mouse platelet aggregation [78].

Omega-3 polyunsaturated fatty acids may have a significant role in the prevention of coronary heart disease. Dietary sources of Omega-3 include fish oils, rich in eicosapentaenoic acid and docosahexaenoic acid, along with plants rich in a-linolenic acid. Randomized secondary prevention clinical trials with fish oils (eicosapentaenoic acid, docosahexaenoic acid) and α-linolenic acid have demonstrated reductions in risk that compare favorably to those seen in landmark secondary prevention trials with lipid-lowering drugs [79].

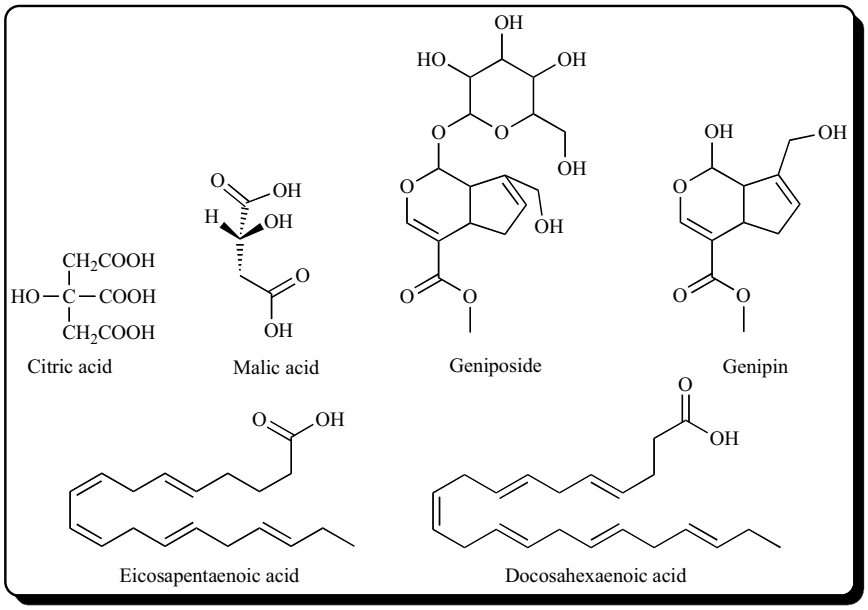
CONCLUSION

Major plants have long been recommended in traditional medicine as a natural cure for the cleansing of blood and treatment of hypertension. Investigation on its mechanisms of action can serve as a potential lead for the development of new antihypertensive agents. Other compounds isolated from plants produced significant coronary dilator action and a protective effect against reperfusion-arrhythmias in the isolated and perfused rat heart. In addition it is well know that the cardiovascular action of calcium antagonist are in wide clinical use as therapeutic agents for the treatment of coro-





nary heart diseases, hypertension etc. The evident chemical diversity of natural products with calcium antagonist activity showed in this review may be due to facts that possess different modes of action. Platelets play a key role in physiological hemostasis and participate in the pathogenesis of thrombosis, this is also an important factor in the angina and myocardial infarction. Hence, agents isolated from plants with anti-platelet and anti-thrombotic effects could have wide therapeutic potential for circulatory diseases.



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Received: 21 January, 2009 Revised: 25 February, 2009 Accepted: 23 April, 2009