December 30, 2020

PharmacologyOnLine

Archives • 2020 • vol.3 • 30-49

NATURAL PLANTS AS THE SOURCE OF EFFECTIVE ANTIHYPERTENSIVE AGENTS- A REVIEW

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Abstract

Hypertension (HTN) or high blood pressure, a metabolic disorder is characterized by the persistently elevated blood pressure in the arteries and it is one of the most common cardiovascular diseases in the world. Although billions of dollars are spent annually for the treatment and detection of cardiovascular disease, current conventional treatments have done little to reduce the number of patients with hypertension. There is an urgent need for treatment of hypertension by exploration of several medicinal plants having potent antihypertensive activity as the modern medicines are having many side effects. Moreover these drugs increase the risk of developing new diseases, making the situation more complicated. Different search engines were explored where importance was given to research article and information presented by authentic organizations and federations. The necessity is to discover and evaluate the unexplored medicinal plants with antihypertensive activities so that they can be used as an alternate of synthetic available medicines. Therefore, the present study aims to investigate and summarize the effect of natural medicinal plant, chemical constituents, plant derived metabolites, plant derived prebiotics and related isolates for the treatment of hypertension considering several factors such as their active agents, therapeutic dosage, side effects, and possible mechanisms in animal and human studies.

Keywords: *Hypertension, cardiovascular diseases, medicinal plants, plant derived metabolites, prebiotics.*

Introduction

Hypertension is a chronic disease in which blood pressure in the arteries is elevated and there are basically two types of hypertension: primary (no medical causes like aldosteronism, renovascular disease, renal failure, and pheochromocytoma) and secondary hypertension (medical causes like endocrine diseases, kidney diseases, glucose tolerance and obesity) [1]. In both situations, the elevated blood pressure is associated with an increased total peripheral resistance that is usually attributable to abnormalities in the sympathetic nervous system and/or the renin-angiotensin-aldosterone system [2]. Hypertension is most common cardiovascular disease and is a major public health issue where more than one-fourth of the world's adult population suffers from arterial hypertension [3,4]. The rate of its prevalence is increasing so rapidly that in 2025 one out of every three adults will be a victim of hypertension [1]. The World Health Organization has reported that high BP is the major cause of death among cardiovascular diseases and it also recognized that more than 50% of people with HTN are unaware of their ailment [5]. Diet, obesity, smoking, alcohol consumption, low physical activity level, stress, and genetic factors are predisposing causes for high BP [6]. Uncontrolled HTN increases the risk of serious health problems and is considered a major risk factor for stroke, heart attack or myocardial infarction (MI), ischemia or brain atrophy, blindness and kidney disease [7]. For available pharmaceutical interventions such as atenolol, amlodipine, diltiazem, losartan, etc., several adverse effects such as tiredness, hypotension, bradycardia, cold extremities, postural hypotension, depression, nausea have been reported [8]. The uses of conventional antihypertensive have been associated with arrays of side effects and there is no cost effective monotherapeutic antihypertensive in use [9]. Regarding the several side effects of pharmacologic agents such as hypotension, orthostatic hypotension, reduced glucose tolerance, increased plasma cholesterol and sexual dysfunction, herbal medicines have been recently much more considered for HTN and cardiovascular diseases management [10]. The ethnobotanical study is an important activity in the area of research and development of drugs since some reports claim that approximately 40% of pharmaceuticals consumed in developed countries come from natural sources, mainly from plants [11]. In the present study, we designed to investigate and summarize the effect of natural medicinal plant, chemical constituents, plant derived metabolites and plant derived prebiotics for the treatment of hypertension considering several factors such as their active agents, therapeutic dosage, side effects, and possible mechanisms in animal and human studies.

Methods

A search (till August 2020) was done in the following databases: PubMed, Springer, Science Direct, MedLine, Scopus, and Google Scholar with the keyword "Natural Plants with Antihypertensive Activity", pairing with 'phytochemicals', 'biological activities/effects', or 'pharmacological activities/effects' and it probable mechanism. No language limitations were forced. Articles were evaluated for the data about the concentrates or divisions and separated mixes of the plant or its parts, fixation or portion (course of organization), test frameworks, results or conceivable system of activity, and last end. Incorporation and avoidance criteria of confirmations found in databases have been given as follows.

Inclusion criteria:

1. Studies carried out in vitro, ex vivo or in vivo with or without using experimental animals, including humans and their consequent tissue and cells;

2. Studies with or without recommending activity mechanisms;

3. Studies with extracts without phytochemical analysis, but having biological activities;

4. Studies with extracts, with phytochemical analysis, but having no report for biological activities.

Exclusion criteria:

1. Duplicate of any data and titles and/or abstracts not meeting the inclusion criteria

Result & Discussion

Medicinal plants used for treatment of HTN in human subjects:

The effect of different medicinal plants used for treatment of HTN along with their part use, dose, and duration, number of subjects used and possible mechanisms of action in human subjects are shown in Table 1. *Hibiscus sabdariffa* L. had a significant lowering effect on arterial BP. Its hypotensive effect may occur through the reduction of vascular reactivity during sympathetic nervous system activation [12]. *Zingiber officinale* lowers SYS and DIA BP and heart rate, although their effects were not statistically significant [13]. *Adenia cissampeloides* (Planch. ex Hook.) decreased the BP significantly by reducing the muscular contraction. It had a very little effect on DIA BP [14]. *Ginkgo biloba* L. had a significant antihypertensive effect (both SYS and DIA BP) but the heart rate statistics were similar in placebo and EGB groups. This medicinal plant had an inhibitory effect on cardiovascular neuroendocrine responses during stress [15]. *Allium sativum* L. lowered DIA BP and inhibited the rate of progression of coronary artery calcification [16]. *Ephedra sp*. had no significant effect on BP, according to the studies [17]. *Coffea arabica* L. decreased SYS and DIA BP during ingestion by this mechanism [18]. *Vitis vinifera* L. or grape juice had no effect while the grape wine indicated a significant lowering effect on BP via decreasing the plasma endothelin-1 concentrations [19].

Reports on phytochemical constituents and antihypertensive properties of plants:

The following medicinal plants were found to be commonly sold for the treatment of hypertension: *Bambusa vulgaris* (Graminaeae), *Bridellia ferruginea* (Euphorbiaceae), *Carica papaya* (Caricaceae), *Mangifera indica* (Anacardiaceae), *Moringa oleifera* (Moringaceae), *Nauclea latifolia* (Rubiaceae), Ocimum gratissimum (Lamiaceae), *Parkia biglobosa* (Leguminosae), *Persea americana* (Lauraceae) shown in Table 2. Published phytochemical investigations of these plants showed that majority of the plants were predominated by the presence of flavonoids, tannins and alkaloids. Most of these herbs were prepared as aqueous decoctions before administration. These plants may need further investigations to identify active principles that can be used to enhance the management of hypertension [20].

Medicinal Plants Used for Management of Hypertension in Nigeria:

Vernonia amygdalina:

Administration of the aqueous extract intravenously in normotensive Sprague-Dawley rats via the femoral vein at doses of 5.0 and 10.0mg/kg caused a bi-phasic alteration of blood pressure, observed as an initial transient rise in mean arterial pressure with a subsequent decline beyond the basal levels [30].

Parinari curatellifolia:

Investigations on the antihypertensive potential of the seed extract revealed that *Parinari curatellifolia* exhibited negative inotropic and chronotropic effects on isolated rabbit heart. A dose-dependent reduction in systolic and diastolic blood pressure, and mean arterial blood pressure were observed in normotensive and salt-induced hypertensive rats [31]. A more recent study investigated the effect of *P. curatellifolia* on doxorubicin-induced cardiovascular diseases in experimental albino rats. Rats administered with Doxorubicin (15 mg/kg) showed significant increase ($P < 0.05$) reduced [32].

Psidium guajava:

Investigated the hypotensive effects of P. guajava leaf aqueous extract (50- 800 mg/kg) in Dahl salt-induced hypertension model in rats. Acute intravenous administrations of the plant extract (50-800 mg/kg i.v.) produced dose-dependent, significant reductions ($p < 0.05$- 0.001) in systemic arterial blood pressures and heart rates of hypertensive rat [33].

Bryophyllum pinnatum:

Aqueous and methanol leaf extracts of the herb were investigated using their effects on arterial blood pressures and heart rates of normotensive and spontaneously hypertensive rats. The extracts at doses of 50-800 mg/kg i.v. or i.p. produced dose-dependent, significant ($p< 0.001 – 0.05$) reduction in

arterial blood pressures and heart rates of anaesthetized normotensive and hypertensive rats [34].

Persea americana:

The aqueous seed extract (AE) of *Persea Americana* at doses of 240, 260, 280 mg/kg were administered to the rats with bolus doses of Ach (1, 2, 4 µg/kg). Pretreatment for 10 consecutive days significantly reduced MAP from 125.7±11.2 to 92.1 ±8.5 mmHg and HR from 274.6 ± 39.3 to 161.6 ±11.6 beats /min [35].

Hibiscus sabdariffa:

The antihypertensive effect of the aqueous extracts of the calyx of H. sabdariffa was investigated in anaesthetized rats. A dose-dependent, but relatively vagal independent decrease in mean arterial pressure was observed in rats. Cumulative doses of the extract in isolated aortic rings precontracted with noradrenaline produced dosedependent relaxation of the rings [36]. A clinical study reported that systolic and diastolic pressure was significantly lowered by 11.2% and 10.7% respectively by day 12 of treatment with *H. sabdariffa* compared to day 0. By day 15, systolic and diastolic blood pressure was elevated by 7.9% and 5.6% respectively [37]. A similar study evaluated the hypotensive effects of aqueous seed extract of this herb in normotensive cat. The study showed the extract significantly lowered cat blood pressure, even at a minimum concentration of 500 µg/ml [38]. Another study attempted to characterize vascular effects of crude extract of dried and powdered calyces of H. sabdariffa on isolated thoracic aorta of male Wistar rats. The crude extract induced mainly endothelium dependent relaxation of aorta which was associated with NOS activation, and also endothelium - independent relaxation associated with activation of smooth muscle potassium channels [39].

Acalypha wilkesiana Hoffmannii:

Graded doses of the aqueous extract of *A. wilkesiana* leaves were administered to rabbits through the auricular vein at a dose of 20 mg/kg produced a substantial decrease in systolic, diastolic and mean arterial blood pressure. The extract at a dose of 10 mg/ml also reduced the rate and force of contraction of isolated rabbit heart [40].

Allium sativum:

Study reported that intravenous injection of A. sativum (5-20 mg/kg) caused a significant ($P<0.05$), dose-dependent decrease in MAP and HR in both the normotensive and 2K1C rats, with more significant effects observed in normotensive rats. And the mechanism of action of *A. sativum* was suggested to probably involve a peripheral mechanism for hypotension [41].

Exploratory studies of some Mexican medicinal plants for hypertension:

Papaveraceae *Argemone mexicana* L., Burseraceae *Bursera simaruba* (L.) Sarg., Acanthaceae *Justicia spicigera* Schltdl. and Selaginellaceae *Selaginella lepidophylla* (Hook. & Grev.) Spring., have been used in Mexican traditional medicine to treat hypertension. Table 3 showed initial values of HR and BP in normotensive and hypertensive rats**.** After oral administration of methanolic extract of each explored plant in normotensive conscious rats all tested extracts decreased the HR, such effect was only observed in hypertensive conscious rats after the administration of B. simaruba; only A. mexicana and B. simaruba decreased the BP after oral administration (Figure 1). All extracts administrated by intravenous injection diminished the mean arterial pressure (Figure 2). Dose response curves to cumulative concentrations of all the extracts promote vascular relaxation in precontracted aortas from rats with and without sugar-induced hypertension [42]. The present study indicated that B. simaruba is worthy of further exploration as a potential phytotherapeutic agent for treating hypertension.

Antihypertensive properties of plant protein–derived hydrolysates and peptides:

During the last decade the *in vitro* capacity of tuber protein -derived peptides to inhibit ACE have gained increasing interest (Table 4). The results demonstrated in Table 4 showed that sweet potato proteins defensin and thioredoxin h2 which were overproduced in Esherichia coli showed moderate ACE-inhibitory capacity (IC50 of 0.190 and 0.152 mg/ml, respectively) and both proteins showed

mixed type inhibitor against ACE using FAPGG as substrate. Hydrolysis with trypsin increased the capacity [43,44]. Several peptides contained in the hydrolysate with IC50 values from 1.31 to 265.43 µM were analyzed. Trypsin inhibitor from the root storage protein of sweet potato, inhibited ACE in a dose-dependent manner (50-200 µg/ml, with 31.9-53.2% inhibition), and the IC50 value was 187.96 µg/ml. After digestion with pepsin the ACE-inhibition increased and peptides were designed by simulating the pepsin cutting sites of sporamin A. Finally, ten new ACE-inhibitory peptides showed IC50 -values from 2.3 to 849.7 µM [45]. Sweet potato protein isolate digested with 16 dierent proteases showed variability in digestibility from 44.7 to 97.3% and IC50 values from 0.16 to 1.08 mg/ml. Based on these results four most potent enzymes (Thermoase PC 10F, Protease S, Proleather FG-F and Orientase 22BF) were selected and combined eect of enzymes were tested. Combination of Thermoase PC 10F, Protease S and Proleather FG-F produced potent ACEinhibition (IC50 of 0.137 mg/ml). Sweet potato protein digest made with combination of three proteases (Thermoase PC10F, Protease S and Proleather FG-F) showed a dose dependent decrease in SBP after single oral administration in SHR [46]. Finally, four different peptides derived from sweet potato storage protein, sporamin, were identified with IC50 values from 9.5 to 300.4 µM [46]. The lowest IC50 values were obtained for synthetic tripeptides, Ile-Thr-Pro (9.5 µM), Gly-Gln-Tyr (52.3 µM) and Ile-Ile-Pro (80.8 µM). Alcalase digests of rapeseed, canola, flaxseed, sunflower seed protein, legumes as well as and mung and chick beans showed high potency for ACE inhibition [47-51,52]. Moreover, Alcalase digestion increased the ACE inhibition of the protein-rich by-product fraction from potato starch industry, potato tuber liquid fraction [53]. For the pea proteins, high ACE-inhibitory activity is reached at the early stage of pepsin hydrolysis and the level is maintained during the small intestine phase using trypsin-chymotrypsin treatment [54]. Study reported moderate antihypertensive effects of an edible tuber *Apios Americana* Medikus in SHR [55]. The antihypertensive effect was suggested to be due to Pro-rich peptides, which were released during digestion.

Pea and mung bean protein digests have been reported to possess antihypertensive activity in SHR [51,56]. Pea protein peptides from *in vitro* gastrointestinal digestion were observed to absorb poorly with *in vitro* model and the hypotensive effect was tested with intravenous administration [57]. Mung bean protein hydrolysate prepared with alcalase decreased significantly SBP (-30.8 mmHg) of SHR 6 h after single oral administration at a dose of 600 mg/ml. The blood pressure-lowering effect continued for at least 8 h, and the blood pressure returned to initial levels at 12 h after administration [51]. The Alcalase-generated rice hydrolysate showed ACE-inhibitory activity with an IC_{50} value of 0.14 mg/ml. A potent ACE-inhibitory peptide with the amino acid sequence of Thr-Gln-Val-Tyr (IC_{50} of 18.2 µM) was isolated and identified from the hydrolysate. Single oral administration of the hydrolysate (600 mg/kg) and Thr-Gln-Val-Tyr (30 mg/kg) showed significantly decreased blood pressure in SHR, -25.6 and -40 mmHg SBP, respectively, after 6h [58].

Antihypertensive properties of plant-based prebiotics:

Various studies have positively found that the consumption of plant-derived prebiotics could exert a protective effect against hypertension. Direct association of prebiotics and antihypertension has been established through various in-vivo trials which is demonstrated in Table 5. Prebiotics have been associated with the promotion of the overall well-being afflicted with blood glucose as well as blood lipid abnormalities, while concurrently exercising positive effect on blood pressure, thus reducing the risk factors of hypertension and coronary heart diseases [61]. In a study evaluating the influence of prebiotics on mice cholesterol found that the supplementation of fructan considerably reduced blood cholesterol by 29.7% ($P<0.001$), LDL-cholesterol concentration by 25.9% ($P<0.01$), IDL-cholesterol level by 39.4% ($P<0.001$) and VLDL-cholesterol concentration by 37.3% ($P<0.05$) compared to the control group [62]. Another study conducted on healthy volunteers found that the daily consumption of 18 gm/day of inulin-supplemented foods significantly reduced plasma total cholesterol ($P<0.02$) and LDL-cholesterol

(P<0.005) by 8.7% (± 3.3) and 14.4% (± 4.3), respectively when compared to the control [63].

However Controversial study showed that consumption of fructooligosaccharides (FOS) enriched cookies (20 g/day) in a double-blind randomized crossover design over 4 weeks in healthy volunteers, the serum triacylglycerol, total- and HDL cholesterol, apoliprotein A-I and B and lipoprotein concentrations persisted relatively constant and did not differ compared to the control [64]. Another study also showed that the cholesterol lowering effect of nondigestible oligosaccharides (NDO) was insignificant [65]

Plant derived flavonoids in regulation of hypertension:

In Table 6, the IC50 values for ACE of most of reported flavonoids have summarized. All most all the subcategories of flavonoids were studied on ACE inhibitory activity. Though the IC50 values for ACE are very greater for flavonoids when compared with antihypertensive drugs, the most of the flavonoids are found to be competitive inhibitors of ACE [71]. The ability to use flavonoids as ACE inhibitors in regulating blood pressure had been studied during the past decades and most of them have proved to be effective in suppressing the activity of ACE [72-74]. The two major flavones of Roxb, apigenin and luteolin, have given a dose dependant enzyme inhibition acitivity. Compared to luteolin aglyconee, luteolin-7-O-glucoside had shown a reduced enzyme activity comprising to a higher IC50 value (Table 6) [75]. A bioassay-guided fractionation of extract of *Sedum sarmentosum* was performed, from where five purified flavonols (Table 6) were found to possess ACE inhibitory activity [76].

Antihypertensive properties of indigenous Lebanese plants:

Table 7 explains a list of total 26 native wild plant species cited by 36 herbalists and traditional healers as "widely used for the treatment of HTN in Lebanon". The value of RFCs (relative frequency) of citation of most (19 out of 26) plants fell in the 0.72–0.95 range, with *M. longifolia*, *U. dioica* and **V. odorata** recording the highest values (0.95) followed by *A. ampeloprasum* (0.94), *A. graveolens* (0.92) *and C. azarolus* (0.90) [80]. As per informants, the perceived aids and safety of cited species were the reasons for their popularity of use. All plant parts appeared to obtain some therapeutic benefits with their leaves and aerial parts recording the highest citations (69.2%, 28.5% respectively). Particularly, decoction was the basic means of preparation (65%) and oral administration at a dosage of 1–3 cups/day for a duration of 3–6 months (90%) was the key application method and the most successful dosage. Numerous previous ethnopharmacological studies have shown that all plants of the list are still being used for the treatment of HTN by many communities in different parts of the world [81-87].

Conclusions

In this study we tried to piece together original information on this subject, so as to raise more awareness, prevent duplication of efforts and possibly bring more attention to medicinal plants as an authentic and effective source of antihypertensive drug. However, these medicinal plants, or plant derived metabolites and the traditional practices are not fully standardized and there are lack of realistic bases for the use of some of these medicinal plants. Hopefully, the outcomes and examined information will encourage researchers to investigate the antihypertensive properties of claimed medicinal plant, chemical constituents, plant derived metabolites, or prebiotics and related isolates to determine the actual mechanism of action and bioactive principle. As the review ended, it was possible to conclude that, still a lot of efforts are compulsory for the corroboration of the plants as well as the identification of the active principles with mechanism of action in these medicinal plants and finally the conduct of clinical trials in humans.

Acknowledgments

The authors are thankful to the Department of Pharmacy, Daffodil International University to give permission and all sorts of supports to conduct the research.

Conflict of Interest

Authors confirmed no conflict of interest

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Table 1. The list of medicinal plants used for treatment of HTN in human subjects

Scientific name	Part	Study design	Does	Jadad score	Groups	Duration	Result	Mechanism of action
Hibiscus sabdariffa L.	Aqueous calyx extract	Uncontrolled trial using cold pressor test	15 mg/kg	0	20 healthy subjects	ND	Elevation of MAP & HR were significantly lower with the extract	Reduction of vascular reactivity during sympathetic nervous system activation
Zingiber officinale Roscoe	Rhizome	Double-blind randomized trial	50, 100 mg/kg	2	Group A: distilled water Group B:100 mg/kg of plant Group C: 50 mg/kg of plant	2-4 h	↓SBP, DBP, HR	Blockade of voltage dependent Ca^{2+} channels
Adenia cissampeloides (Planch. ex Hook.) Harms	Extract	Single-blind trial	150 mg/kg	0	14 patients Group A: Test group Group B: Control group	1 year	↓BP with little effect on SBP	Reduction in muscular contraction
Ginkgo biloba L.	Leaf	Double-blind, placebocontrolled trial	120 mg	1	70 patients	Singledose adminis tration	↓SBP & DBP No significant effect on HR	Inhibition of cardiovascular neuroendocrine responses during stress
Hibiscus sabdariffa L.	Calyx	Randomized uncontrolled trial	15 mg/kg	1	20 healthy subjects	ND	↓MAP	Reduction of vascular reactivity during sympathetic nervous system activation
Allium sativum L.	Bulb	Placebocontrolled, double-blind, randomized trial	1000 mg	2	210 patients: 106 test 106 placebo	1 year	↓DBP	Inhibition of artery calcification rate
Coffea arabica L.	Been	Placebocontrolled, randomized, double-blind trial	140 mg/kg	2	28 patients: 14 placebo 14 test	14 w	↑BP Useful for mild hypertensive patients	NO-mediated vasodilation

Ephedra sp.	Sprout	Double-blind, randomized, placebocontrolled	15 mg extract 60 mg caffeine	2	13 healthy subjects	7 d	No significant change in any cardiovascular parameter	ND
Vitis vinifera L.	Seed	Double blind placebo-controlled randomized	300 mg/d	2	70 patients: 35 placebo 35 test	8 w	↓3.0 mmHg for SBP & 1.4 mmHg for DBP No significant change in ABP	NO synthesis dependent pathway Relaxes the smooth muscles on vessels

LDH=Lactate dehydrogenase, CK=creatine kinase, DBP=diastolic blood pressure, SBP=systolic blood pressure, ABP=arterial blood pressure, eNOS= endothelial nitric oxide synthase, MAP= mean arterial pressure, D= day

Table 2. Reports on phytochemical constituents and antihypertensive properties of plants [20-29]

Plant species	Documented phytochemical properties	Documented antihypertensive activity
Bambusa vulgaris	The aqueous extract of *B. vulgaris* leaves is reported to contain alkaloids, tannins, phenolics, glycosides, saponins, flavonoids, and anthraquinones.	Asian medicine, especially in China and Japan have recorded Bamboo to be protective against cardiovascular diseases.
Bridellia ferruginea	The phytochemical analysis carried out on *B. ferruginea* leaves and bark detected the presence of alkaloids, flavonoids, tannin, cardiac glycosides, anthraquinone, phlobatinnin, and saponins, and was negative for anthocyanin .	Studies by Tettey-Larbi et al. [20] recorded high activity and concentration of Potassium-40 in *B. ferruginea* and stated that this medicinal plant can significantly aid the therapeutic purposes for the treatment of hypertension.
Carica papaya	The leaves of *C. papaya* are rich in flavonoids (kaempferol and myricetin), alkaloids (carpaine, pseudocarpaine, dehydrocarpaine I and II), phenolic compounds (ferulic acid, caffeic acid, chlorogenic acid), cynogenetic compounds (benzylglucosinolate), carotenoids and anthraquinones glycoside.	*C. papaya* plant (leaves and unripe fruits) have been used in treating numerous diseases including high blood pressure.
Nauclea latifolia	Phytochemical screening of different parts of the plant confirmed the presence of saponins, alkaloids, glycosides, tannins, flavonoids and anthraquinones.	Roots of *N. latifolia* are used in Nigeria for the treatment of hypertension. The extract reduced systolic, diastolic, and mean arterial pressure in normotensive and in one kidney one clip hypertensive rats in a dose dependant manner.
Mangifera indica	Phytochemical screening of the leaves revealed the presence of saponin, steroids, tannin, flavonoid, reducing sugars, cardiac glycosides and anthraquinone.	Various biological effects including its hypolipidemic activity have been studied. Anecdotal reports have however stated its use in the management of hypertension.

Moringa oleifera	The foliage of *M. oleifera* has been established as a rich source of phenolic acids, flavonoids, alkaloids, phytosterols, natural sugars, vitamins (ascorbic acid, tocopherol, folate) minerals, organic acids and polyunsaturated fatty acids.	Oral administration of *M. oleifera* seed powder in spontaneous hypertensive rats resulted in a beneficial effect on the cardiac structure and function. This study thus provided scientific rational for the empirical use of moringa in traditional Malagasy medicine against cardiac diseases associated with blood pressure overload.
Ocimum gratissimum	Phytochemical screening revealed the presence of alkaloids, tannins, saponin, steroids, cardiac glycoside, flavonoids, terpenoids and phenols. The proximate analysis confirmed that the leaves contain appreciable amount of ash, crude protein, lipids, fibre and carbohydrates.	Treatment of deoxycorticosterone acetate-hypertensive rats with the essential oil of *Ocimum gratissimum* caused a dose-dependently decreased in blood pressure.
Parkia biglobosa	Phytochemical screening showed that sterols and triterpenes, saponosides, tannins, coumarins, anthocyanosides and flavonosides are present in both bark and leaf but in different concentrations	*P. biglobosa* seeds and bark are used in Burkina Faso in West Africa for the treatment of hypertension.
Persea americana	Peptone, b-galactoside, glycosylated abscisic acid, alkaloids, cellulose, polygalacto urease, polyuronoids, cytochrome *P*-450 and volatile oils are reported to be present in this plant.	This plant is reported to be used in the treatment of hypertension.

Table 3. Initial values of HR and BP in normotensive and hypertensive rats

Group	BP	**BP**	**HR**	**HR**
	Normotensive	**Hypertensive**	**Normotensive**	**Hypertensive**
Control	104±1	139±3	358±2	370±7
Argemone mexicana	114±2	138±2	329±4	354±5
Bursera simaruba	115±3	144±2	304±5	336±9
Selaginella lepidophylla	114±2	136±6	371±5	398±6
Justicia spicigera	107±1	136±1	327±8	376±3

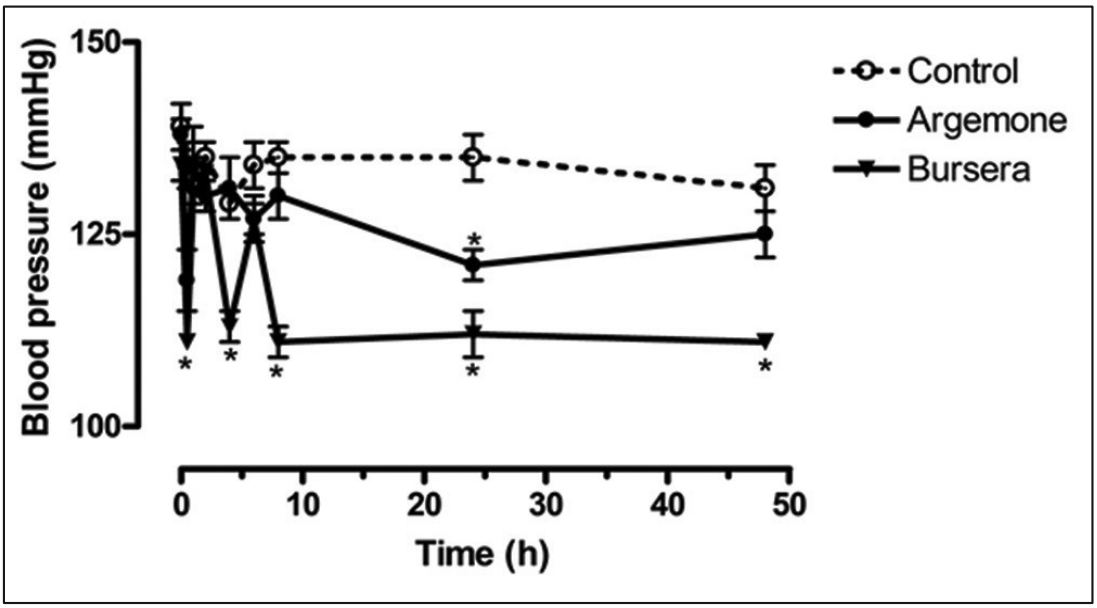

Figure 1. Influence of a single oral administration of *Argemone Mexicana*, and *Bursera simaruba* over blood pressure in hypertensive rats

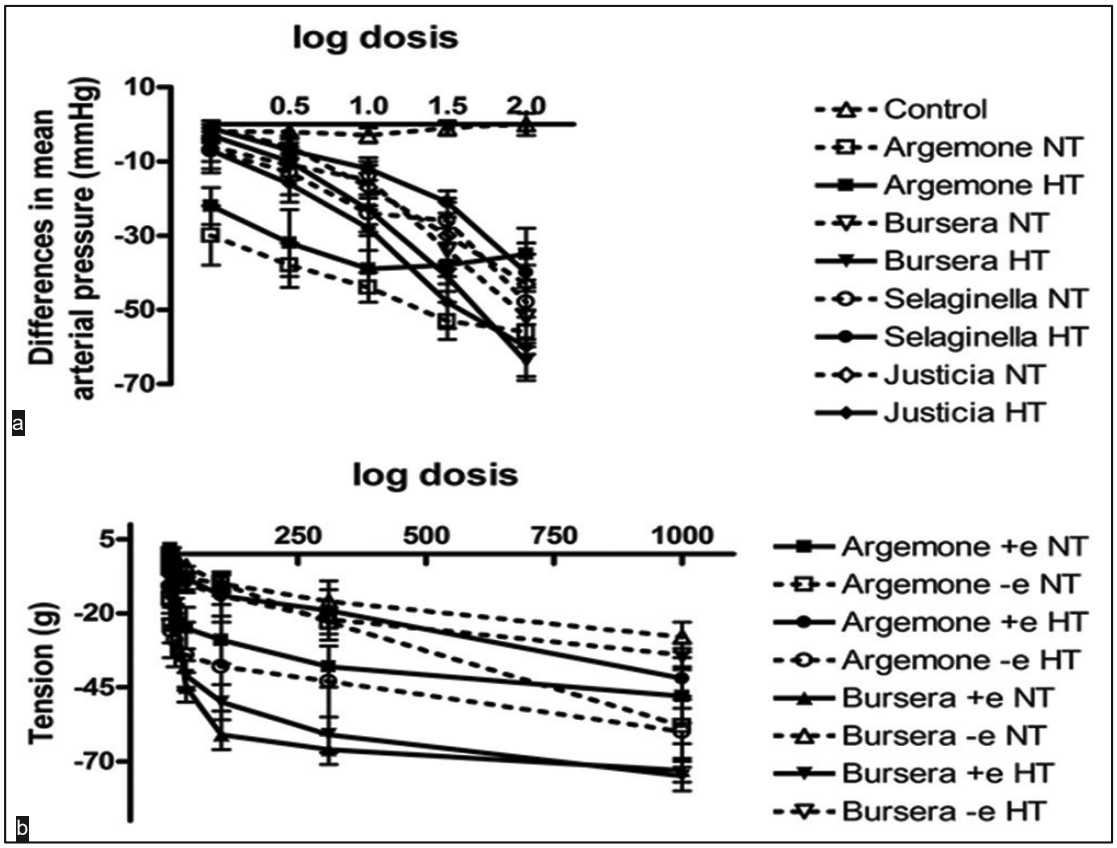

Figure 2. (a) Influence of intravenous administration of *Argemone mexicana*, *Bursera simaruba*, *Selaginella lepidophylla* and *Justicia spicigera* over mean arterial pressure in normotensive and hypertensive rats. (b) Aortic vascular reactivity due increasing concentrations of A. mexicana and B. simaruba in normotensive and hypertensive rats.

Table 4. ACE-inhibitory activities in vitro and antihypertensive effect in vivo of plant protein–derived hydrolysates and peptides

Source protein	Enzyme or other process conditions	ACE inhibition	Identified peptides		In vivo response		Ref.
		IC50 (mg/ml)	Sequences	IC50 value (μM)	Dose administration model	Response (Δ SBP mmHg)	
Sweet potato tuber protein isolate	Thermoase PC 10F, Protease S & Proleather FG-F	0.018	ITP IIP GQY STYQT	9.5 80.8 52.3 300.4	500 mg/kg hydrolysate, oral, SHR	-30 after 8 h	[46]
Sweet potato tuber defensin	Trypsin	0.190	GFR FK IMVAEAR GPCSR CFCTKPC MCESASSK	94.25 265.43 84.12 61.67 1.31 75.93			[43]
Sweet potato tuber Thioredoxin h	Trypsin	0.152	EVPK VVGAK FTDVDFIK MMEPMVK	1.73 1.14 0.42 1.03			[44]
Sweet potato tuber Trypsin inhibitor	Pepsin	0.188	HDHM LR SNIP VRL TYCQ GTEKC RF VKAGE AH KIEL	276.2 746.4 228.3 208.6 2.3 275.8 392.2 141.56 523.5 849.7			[45]
Sunflower protein	Alcalase Peptide fraction from affinity purification	0.062 $1.18x10^{-3}$					[59]

Pea protein	Gastrointestinal digest in vitro	0.070			50 mg/kg intravenous, SHR	-44, transient and sharp reduction	[57]
Apios Americana Medikus tuber	Water extract (rich in proline)	127			200 mg/kg oral, SHR	-25 after 0.5 and 1 h	[55]
Mung bean protein	Alcalase, 6kDa MWCO permeate	0.64	KDYRL VTPALR KLPAGTLF	26.5 82.4 13.4	600 mg/kg oral, SHR	-30.8 after 6 h	[51,52]
Rice	Alcalase	0.14	TQVY	18.2	600 mg/kg hydrolysate 30 mg peptide/kg SHR, oral	-25.6 after 6 h -40 after 6 h	[52,58,60]

ISSN: 1827-8620

Table 5. Antihypertensive effects of plant derived prebiotics

Intervention	Experimental design	Subjects	Dose	Effects	Ref.
Soluble fiber extracted from oat bran	Randomized, double-blind, placebo-controlled	n=110; 30 to 65 years; not on hypertension treatment; SBP of 125-159 mmHg and DBP of < 95 mmHg	8 g/d of fiber for 12 weeks	A reduction in SBP of 2.0 mmHg and DBP of 1.0 mmHg	[66]
Beta-glucan from whole oats cereals	Randomized, parallel, pilot trial	n=18; 27-59 years old; healthy, untreated hypertensives with SBP of 130-160 mmHg and DBP of 85-100 mmHg	5.52 g/d of betaglucan for 6 weeks	A reduction in SBP of 7.5 mmHg and DBP of 5.5 mmHg	[67]
Diet containing soy protein isolate and supplementation of fiber extracted from psyllium	Randomized, double-blind, parallel	n=36; nonsmoking men or women > 20 years old; on antihypertensive drug therapy for > 6 months; SBP of 130160 mmHg	12 g fiber/d for 8 weeks	A reduction in SBP of 5.9 mmHg	[68]
Dietary fiber in the form of pill supplementation	Randomized, double-blind, parallel, placebocontrolled	n=63; 18-70 yrs old; hypertensive with a minimum DBP of > 90 mmHg	7 g/d of dietary fiber for 12 weeks	A reduction in DBP of 5 mmHg	[69]
Bread substituted with lupin kernel flour	Randomized, parallel	n=74; 20-70 years old; overweight and obese men and women with BMI of 25-35; SBP<150 mmHg and DBP<95 mmHg	4 x 40g of bread/d for 16 weeks; Bread contained 9.5% w/w of fiber	A reduction in SBP of 3.0 mmHg	[70]

Table 6. IC50 values of ACE inhibitory flavonoids and their metabolites

Group of Flavonoids	Compound	IC_{50} Value	Ref.
Anthocyanins	Delphinidin-3-*O*-sambubioside	142 µM	[72]
	Cyanidin-3-*O*-sambubioside	118 µM	[72]
	Cyanidin-3-*O*-β-glucoside	139 µM	[74]
Flavones	Apigenin	280 µM	[75]
	Luteolin	290 µM	[75]
	Luteolin-7-*O*-glucopyranoside	280 µM	[75]
Flavonols	Quercetin glucuronide	200 µM	[77]
	Quercetin-3-*O*-(6″-galoyl)-galactoside	160 µM	[77]
	Quercetin-3-O-α—(6‴-caffeoylglucosyl-β-1,2-rhamnoside)	159 µM	[76]
	Quercetin-3-O-α—(6‴-p-coumaroylglucosyl-β-1,2- rhamnoside)	352 µM	[76]
	Isorhamnetin-3-β-glucopyranoside	409 µM	[76]
	Quercetin-3-β-glucopyranoside	709 µM	[76]
	Quercetin-3-α-arabinopyranoside	310 µM	[75]
	Kaempferol-3-α-arabinopyranoside	393 µM	[76]
Flavan-3-ols	Epicatechin - dimer	97 µM	[78]
	Epicatechin - hexamer	8 µM	[78]
Chalcones	Butein	730 µM	[79]

Table 7. Plant species and traditional practices used for the treatment hypertension in Lebanon.

Plant Species (Family)	English Name	Arabic Name	Preparation and Administration	RFCs
Allium ampeloprasum L. (Amaryllidaceae)	Leek	Kerrat	Decoction of bulbs and leaves, 1 cup/day. Medicinal food	0.94
Apium graveolens L. (Apiaceae)	Wild Celery	Krafs	Fresh juice of shoots and leaves, 1 cup twice/week	0.92
Artemisia herba alba Asso (Asteraceae)	White Worm-wood	Shieh	Infusion of aerial parts, 1 cup/day	0.64
Asparagus acutifolius L. (Asparagaceae)	Wild Asparagus	Halyoun	Decoction of stem tops, 1 cup/day	0.90
Calicotome villosa (Poir.) Link (Fabaceae)	Spiny broom	Kandoul	Decoction of seeds, 1 cup/day	0.35
Centaurium erythraea Rafn (Gentianaceae)	Spiked centaury	Kantarioun	Infusion of flowering aerial parts, 3 cups/day for 2 weeks	0.55
Crataegus azarolus L. (Rosaceae)	Hawthorn	Zaarour	Decoction of leaves, flowers or fruits 1 cup/day	0.90
Cupressus sempervirens L. (Cupressaceae)	Cypress	Sarou	Decoction of leaves, 1 cup/day	0.45
Equisetum telmateia Ehrh. (Equisetaceae)	Branched horsetail	Zanab El-khayl	Aerial parts Infusion/3cups/day for 8–12 weeks	0.75
Eryngium creticum Lam. (Apiaceae)	Eryngo	Kers Aanni	Juice of young shoots and leaves, ½ cup/day	0.80
Foeniculum vulgare Mill	Fennel	Choumar	Decoction of seeds, 2 cups/day	0.65
Fibigia clypeata (L.) Medik. (Brassicaceae)	Roman Shields	Hachichet El Oumeh	Infusion of leaves, 1cup/day	0.90
Hordeum vulgare L. (Poaceae)	Barley	Sha'ir	Decoction of seeds, 1 cup/day	0.94
Laurus nobilis L. (Lauraceae)	Sweet bay	Ghar	Decoction of leaves, 1/2 cup/day	0.89
Matricaria aurea (Loefl.) Sch.Bip. (Compositae)	Chamomile	Bebounej	Infusion flowers, 3 cup/day as herbal tea	0.85
Matricaria chamomilla L. (Asteraceae)	Chamomile	Bebounej	Infusion of flowers, 3cup/day	0.85
Mentha longifolia L. (Lamiaceae)	Horse Mint	Na'na'a	Infusion of leaves, 2cup/day	0.95
Melissa officinalis L. (Lamiaceae)	Lemon Balm	Mallieseh	Infusion of leaves, 2cup/day	0.45
Myrtus communis L. (Myrtaceae)	Myrtle	Hemblas	Maceration of fresh fruits in oil, essential oil	0.86
Paronychia argentea Lam. (Caryophyllaceae)	Silvery Paronychia	Hachichet El Ramel	Decoction of aerial parts, 1 cup/day	0.40
Peganum harmala L. (Nitrariaceae)	Syrian rue, harmel	Harmala	Decoction of aerial parts, 1 cup/day	0.72
Plantago major L. (Plantaginaceae)	Broadleaf plantain	Lissan el Hamal	Decoction, 1 cup/day	0.89
Portulaca oleracea L. (Portulacaceae)	Purslane	Bakleh	Decoction of leaves, 3 cups/day	0.88
Raphanus raphanistrum L. (Brassicaceae)	Wild radish	Fejel Barie	Juice of aerial parts, roots Fresh ½ cup/day	0.94
Urtica dioica L. (Urticaceae)	Stinging nettle	Korrays	Decoction of young shoots and leaves, 3 cups/day	0.95
Viola odorata L. (Violaceae)	Sweet violet	Banafsaj	Infusion of flowers., 3 cup/day	0.95

RFC: relative frequency of citation.