Treatment of Hypertension by Using Natural Herbs and their Mechanism of Action

Bandar Hamad Aloufi*, Mohammad Ali Atwan, Ahmed Mohajja Alshammari

Received: 29 March 2022 / Received in revised form: 31 May 2022, Accepted: 02 June 2022, Published online: 11 June 2022

Abstract

The medical term used for blood pressure is Hypertension (HTN). Hypertension is a common problem faced by most people today. The leading danger for many diseases such as CVD (cardiovascular) disorder and stroke is high blood pressure. Major diseases like CHF (congestive heart failure), renal disease and blindness can also be caused by HTN. Awareness of plant-based medication therapeutics is continuously increasing day by day. Different substitute medicaments such as a proper and balanced diet, herbs, exercise, supplements, stress and supervision help lower HBP (high blood pressure). Recent studies found that various treatments are successful in HBP, including diet, exercise, management, herbs, and supplements. Plants consist of abundant phytochemicals that have substantiated with evidence to be defensive against cardiovascular diseases. Using plant-based natural compounds as protective and anti-hypersensitive agents is an exciting strategy for exploring biotic products. Plants are rich in many secondary metabolites, such as flavonoids, alkaloids, and carotenoids, and have been found to exert antihypertensive effects in vivo. For high blood pressure, knowledge acquisition is carried out on herbal medicines every year. For HBP treatment, there are numerous herbal medicines, including Arjuna, Ginseng, Ginger and Garlic, which can be securely used to handle hypertension.

Keywords: HTN, CVD, Natural products, Antihypertensive herbal plants

Introduction

Blood vessels and heart disease (Cardiovascular disease) are the chief factors of death and account for about one-third of deaths worldwide (Lopez *et al.*, 2021). Most of these events are brought about not only by cardiovascular peril agents but by numerous other factors (Nowbar *et al.*, 2019). The most significant of these are hypertension (HTN) in industrialized countries and blood lipids of high level, corpulence, smoking, age, glucose intolerance, and physical inactivity (Mohsen Ibrahim, 2018). Hypertension is undoubtedly a modifiable risk factor. From hypertension, approximately one billion persons suffer, including 26% adult

Bandar Hamad Aloufi*, Mohammad Ali Atwan, Ahmed Mohajja Alshammari

Department of Biology, College of Science, University of Ha'il, Ha'il 2440, Saudi Arabia.

*E-mail: b.alofi@uoh@edu.sa; Bandaraloufi@yahoo.com

population worldwide (Oliva, 2019). It is estimated that the number of patients affected with hypertension will reach up to 29% of the population by 2025 as they increase every year. The total amount of affected hypertension in adults was 972 million; in developed countries, it is 333 million, and in developing countries, 639 million. In 2025, the number of adults with hypertension is estimated to enhance by 60% to 1.56 billion people (Mills *et al.*, 2020). HBP is a medical condition in which blood pressure is lingeringly increased. HBP is the most common type of hypertension. It has been the most important public health and medical problem worldwide in the last few years (Akbarpour *et al.*, 2018). Hypertension seems to be the most significant danger for developing CAD (coronary artery disease) and cardiovascular disorders.

High blood pressure (140mmHg) and diastolic blood pressure (90 mmHg) are also recognized as HBP. Blood pressure used in ESH / ESC 2007, optimal groups (diastolic-blood-pressure below 80mmHg and systolic-blood-pressure below 120-mmHg), normal (diastolic-blood-pressure 80-840 and systolic-blood-pressure 120-129 mmHg) (Fuchs & Whelton, 2020). Separate groups for grade hypertension and isolated systolic hypertension (130-139 mmHg and 85-89 mmHg diastolic blood) are developed with high quality after high normality (Tanaka, 2020). There are 3 degrees of hypertension corresponding to 1st mild (diastolic-blood-pressure 90-99 mmHg and systolic-blood-pressure 140-159 mmHg), 2nd Moderate (diastolic-blood-pressure 100-109 mmHg and systolicblood-pressure 160-179 mmHg), 3rd severe hypertension (110 mmHg or more diastolic-blood-pressure) and (180 or more systolic-blood-pressure) (Roerecke et al., 2019). Isolated systolichypertension (140 mmHg or more systolic-blood-pressure) is classified as 1st, 2nd or 3rd depending upon systolic-bloodpressure level, providing that the diastolic blood pressure is below 90 mmHg. When systolic blood pressure and diastolic blood pressure fall into different groups, the rich category assesses total cardiovascular disorder. However, there are two types of HBP: primary hypertension and secondary hypertension. Secondary hypertension, affecting 5 to 10% of people with hypertension, is caused by conspicuous diseases like renal injury and diabetes and has a relatively greater chance of receiving treatment (Jennings et al., 2021). In contrast, many agents obtain fundamental hypertension such as diet, age, lifestyle, neurohumoral activity, and interactions. Management of essential hypertension is more difficult because it may be more difficult to determine its etiology (Martinez-Ríos et al., 2021). Interestingly, the percentage (90-95%) of patients with serious hypertension exceeds the percentage



© 2022 The Author(s). This is an **Open Access** article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0). https://creativecommons.org/licenses/by/4.0/deed.en of patients with secondary hypertension (Boa Sorte Silva *et al.*, 2021). Menace agents for heart attack, heart failure, and arterial aneurysms are permanent HTN(hypertension) stroke and are one

of the prime reasons for immedicable renal disease (Surma *et al.*, 2021). Graphical interphase and the role of natural phytochemicals in hypertension are indicated in **Figure 1**.

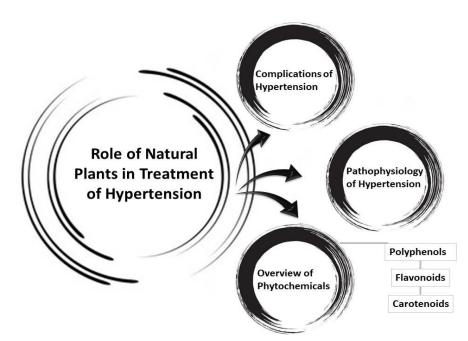


Figure 1. Graphical view of the effect of natural plants on hypertension treatment

Role of Natural Plants in Hypertension Treatment

From a particular time until the commencement of highly developed social and economic structure, the oldest friends of humanity are plants (Diop et al., 2022). Despite giving shelter and food, it is also a good source of medication and has been accustomed to healing abilities and pain-relieving. Even today, people depend heavily on the healing potential of plants in semiurban and rural areas (Khattulanuar et al., 2022). According to the WHO (World Health Organization), approximately three-quarters of the world's population is dependent on traditional medicines for health care. Natural products from plant resources play an important role in improving human health quality in many parts of the world (Bell et al., 2019). Consumption of natural products is important for treating many fatal diseases because they have not been shown to produce toxic effects (Xiang et al., 2018). A large number of scientific literature provides evidence of the ethnopharmacological use of various medicinal plants against various diseases. Because of economic factors, nearly 80% of the population in developing countries still use plant extracts as a drug. A moderate rise in blood pressure reduces life (Zheng et al., 2020). Improvement in BP reduction and control in the peril of related health problems can be done by medications, as well as changes in diet and lifestyle

Complications of Hypertension

This disease does not show any early symptoms and eventually is the utmost significant cardiovascular risk factor, also known as silent kills (Artru *et al.*, 2022). Heart attack, congestive heart failure, stroke, chronic kidney disease (hypertensive nephropathy), hypertensive-retinopathy, left-ventricular enlargement, and aneurysm (Aspite et al., 2022). Blood pressure and thus increased heart rate or prolonged hypertension, associated vascularizing and subsequent atherosclerosis are linked to issues with hypertension (Gupta et al., 2022). Accelerated atherosclerosis is accompanied by vascular and cardiac or prolonged hypertension. Hypertension is a major risk factor for causing coronary-artery abnormalities, Hypertrophy of the left ventricular, diastolic dysfunction and systolic dysfunction. It is regarded as a heart disease with hypertension that potentially causes heart failure (Denisova et al., 2022). Microcirculation is affected by hypertension, while accelerates atherosclerosis in large vessels (epicedial) are also affected by hypertension. Atherosclerosis has a great risk factor for creating direct injuries from mechanical stress in endothelial cells. High blood pressure can change permeability and enable the transport of additional lipoproteins to intact endothelial wall cells (Bailey et al., 2022).

Pathophysiology of Hypertension

Hypertension (HTN) mechanism is not fully understood, especially for essential hypertension (Webb & Werring, 2022). Hypertension is a disorder of blood regulation; the failure of the kidneys to secrete sodium promotes the excretion of natriuretic factors like atrial natriuretic factor; The overactive reninangiotensin system causes vasoconstriction and accumulation of sodium and water (Chia, 2022). Blood volume development contributes to HTN. The sympathetic, hyperactive nervous system raises stress (Ekblad *et al.*, 2022). HTN is considered to be inherited and polygenic (caused by more than one gene), and some candidate genes are thought to be etiologically present in this condition (Figure 2).

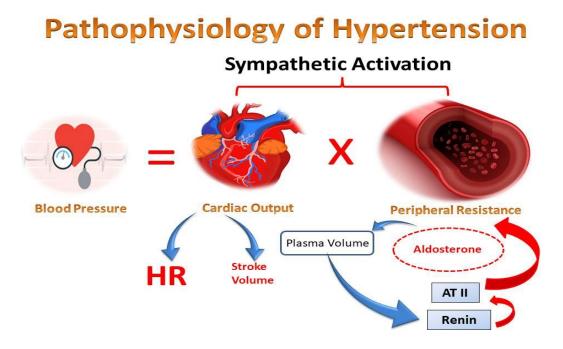


Figure 2. Pathophysiology of Hypertension

Overview of Phytochemicals

The scientific foundation essential for the formation and invention of novel drugs from a natural source is provided by the chemical characterization and analysis of the plant materials composition. Phytochemicals are natural compounds in fruits, vegetables, aromatic plants, leaves, medicinal plants, flowers, and roots (Shaikh & Patil, 2020; AlHumaidi *et al.*, 2022). Based on their application in plant metabolism, these are characterized as primary metabolites (proteins, carbohydrates, and lipids) and secondary metabolites (steroids, polyphenols, alkaloids, and carotenoids) (Ike, 2020). This review sums up the existing evidence for the impact of photochemistry on blood pressure (Mondal & Rahaman, 2020). Excessive consumption of fresh vegetables and fruits is likely associated with a lower risk of death related to hypertension prevention.

Polyphenols and Hypertension

Polyphenols are natural plant compounds present in plant food (vegetables, fruits, dark chocolate, tea, spices, wine, and herbs) (Liu *et al.*, 2019). They neutralize the damaging free radicals that harm your cells and enhance your risk of conditions like diabetes, cancer, and cardiovascular disease (Waśkiewicz *et al.*, 2019). Polyphenols are secondary metabolites of aromatic plants that spread widely throughout the herb kingdom. They have an aromatic benzene ring carrying one or more hydroxyl substituents derived from the Shikimate pathway or phenylpropanoid metabolism. Above 8000 polyphenol structures have been recognized so far. Polyphenol compounds include Caffeic acid, Chromogenic acid, Gallic acid, Coumaric acid, Ishamhamnetin, Quercetin, Naringenin, Kaempferol, Floretin, Enterolactone, Enterodiol, and Hesperetin (Durazzo *et al.*, 2019). Thanks to its antioxidant effects and its ability to activate vascular endothelial nitric oxide synthase, polyphenols increase the bioavailability of endothelial nitric oxide and reduce blood pressure.

Flavonoids and Hypertension

Flavonoids are abundant in dietary plants and herbs. Regular consumption of flavonoids has reduced the onset or progression of many cardiovascular diseases, especially hypertension (Maaliki *et al.*, 2019; Alhazmi *et al.*, 2022). Flavonoids compound contains flavones and isoflavones. They have a high concentration in foodstuff like fruits, vegetables, legumes, grains, and soy. Polyphenolic compounds have much influence on the color and flavor of these foods. Flavonols flavones and isoflavones are famous for their hormonal activity but they are also potent antioxidant and tyrosine kinase inhibitor.

Carotenoids and Hypertension

Pigmented compounds family is synthesized by carotenoid plants and microorganisms but not from the animals. In plants, carotenoids contribute to photosynthetic machines and guard them against photographic harm. The main carotenoid sources in human nutrition are fruits and vegetables (Ahmad *et al.*, 2022). Carotenoids are present as a mini component in fruits and vegetables and also responsible for their colors red, yellow and orange. They are considered responsible for the beneficial property of vegetables and fruits in preventing human diseases like cardiovascular diseases (Toh *et al.*, 2021).

Naturally occurring herbs and medicinal plants having antihypertensive potential / Back to nature

Over the past decade, herbal remedies have been used as a method of treatment that has increased remarkably. Having less

Table 1. Herbal drugs used for the treatment of hypertension

undesirable side effects, herbal medicine is a low-priced alternative (Thomas *et al.*, 2021). Herbs and herbal remedies are not surprising because they contain thousands of bioactive components whose therapeutic applications are known (Alotiby & Al-Harbi, 2021). Herbs are used as pharmaceutical drugs providing a starting point for synthesizing more than 50%. Validation of these drugs will increase the trust of traditional drug users and cause suspicion of synthesized drugs. For the treatment of hypertension, many herbal drugs are used (Table 1).

Botanical Name	Common Name	Family	Chemical Constituent	Reference
Allium Sativum	Garlic	Liliaceae	Sulfur-Containing Compounds Alliin, Ajoene, Diallyl sulfide, Dithiin, Sallylcysteine,	(Agrawal <i>et al.</i> , 2010)
Withania Somnifera	Ashwagandha	Solanaceae	Alkaloids Including Withanine, Withananine, Withananinine, Pseudowithanine, Somnine, Somniferinine, and Somniferine. The Leaves Of Indian Chemo Type Contain Withanolides, Including Withaferin A.	(Kushwaha et al., 2012)
Hibiscus Sabdariffa	Hibiscus	Malvaceae	Andhibiscic, Oxalic, Citric, Malic, Tarteric Acid	(Ajay <i>et al.</i> , 2007)
Ephedra Sinica, Ephedra Intermedia Or Ephedra Equisetina.	Ma Huang (Herbal Ephedra	Ephedraceae	Contain The Phenylproamine Alkaloids, L-Ephedrine, And Pseudoephedrine. E. Sinica Contains 55-78% Ephedrine And 12-23% Pseudoephedrine.	(Agrawal <i>et al.</i> , 2010)
Angelicae Gigantis	Chinese Angelica	Apiaceae	Root Contains Ferulic Acid, About 0.2-0.4% Of Essential Oil, Ligusticide, Brefeldin A, Nicotinic Acid, Angelicide, Succinic Acid, Butylphthalide, and Several Coumarin Constituents.	(Agrawal <i>et al.</i> , 2010)
Coleus Forskohlii	Forskolin	Lamiaceae.	Ditermene Coleonol,	(Jagtap <i>et al.</i> , 2011
Vitis Vinifera	Raisins	Vitaceae	Grape Skin Produces Endothelium Dependent Aorta Relaxation Possibly By Its Flavonoids (Quercetin)	(Nassiri-Asl & Hosseinzadeh,2016
Panex Ginseng	Ginseng	Araliaceous	Ginsenoside	(Nagar et al., 2020)
Hypericum Perforatum	St.John's Wort	Hyperi -Caeca	Hype Ricin And Hyperfine	(Villegas & Le, 2019)
Lorentus Ben- Winces	African Milestone	Lorentheacae	Tender Shoots—Contain 10% Tannins	(Shrout <i>et al.</i> , 2017
Cystisus Scoparius	Scotch Broom	Papilionaceae	 Quinolizidine Alkaloids; Main Alkaloids Are (-)-Lupanine, Sparteine, Ammodendrine And Various Derivatives; Biogenic Amines, Including Try Amine, Dopamine; Epinine, Is Flavone Glycosides Including Scoparin; Genistein, Essential Oil; Flavonoids; Caffeic Acid And P-Coumaric Acids; Tannins. Seeds Contain Lectins 	(Giles <i>et al.</i> , 2018)
Cimicifuga Racemosa	Black Cohosh	Ranunculaceae	Triterpene Glycosides,Cycloartanes	(Giles et al., 2018)
Uncaria Tomantosa	Cat's Claw	Rubeacae	Rhynchophylline, Hirsutine, And Mitraphylline. Rhynchophylline. Three Sterols — Beta Sitosterol (80%), Stigma Sterol, And Campestral—	(Yang, 2019)

Nelumbo Nucifera	Lotus	Nelumbonaceae	Alkaloids Including Isoliensinine, Liensinine, Lotusine, Referine, and Demethylcoclaurine. And Methylcorypalline, Among Them, Referine has been indicated to have A Vasodilating Effect, And Liensinine Has Antihypertensive And Antiarrhymic Abilities	(Mumtaz <i>et al.</i> , 2017)
Gingiber Officinalis	Ginger	Zingiberaceae	Volatile Oil 3sesquiterpines: Bisaboline, Zingiberene And Zingiberol	(Baharvand-Ahmadi & Asadi-Samani, 2017)
Ginkgo Biloba	Ginkgo	Ginkgoaceae	Hydroginkgolic Acid, Phenolic Acids; Ginkgoides Flavonoids Ginkgolic Acid, . Bioflavonoids; Bilobetin Ginkgetin, Sciadopitysin,	(DalBó & de Aguiar Amaral, 2017)
Hydrastis Canadensis	Golden Seal	Ranunculaceae	3 Alkaloid Hydrastine, Berberine, Canadine	(Agrawal <i>et al.</i> , 2010)
Crataegus Laevigata/ Crataegus Oxycantha	Hawthorn	Rosaceae	Catechins, Flavonoids, Saponins, Triterpene Amines, And Oligomeric Proanthocyanidins (Opcs	(Chang et al., 2005)
Viscum Album	Mistletoe	Loranthaceae	Toxic Proteins, Viscotoxin Designated Phoratoxin,	(Ofem et al., 2007)
Urtica Dioica	Stinging Nettle	Urticaceae	Histamine, Acetylcholine, And 5hydroxytryptamine (5-HT). Acetylcholine Is Present In The Rhizomes And Cortex, Leaves, and Rootlets, In The Ascending Order Of Concentration.	(Qayyum <i>et al.</i> , 2006)
Centella Asiatica	Jalbrahmi	Apiaceae	Pentacyclic Triterpenes Derivativesmadecassosides And Asiaticosides.	(Nisha et al., 2017)
Nigella Sativa	Black Cumin Seeds	Ranunculaceae	Dithymoquinone Thymoquinone, , Thymol, Caracole, Thymohydroquinone, Tanethole And 4-Terpineol.	(Vaz <i>et al.</i> , 2018)
Termenalia Arjuna	Arjuna	Combretaceae.	Triterpenoid Saponins, Flavonoids, Tannins, Ellagic Acid, Phytosterols, Gallic Acid, Magnesium, Opcs, Zinc, Calcium, And Copper	(Dhingra <i>et al.</i> , 2013)
Rauwolfia Serpentina	Sankroot	Apocynaceae	Rescinnamine, Serpentinine, Deserpidine, Sarpagine, Ajmaline, And Chandran	(Oates, 2001)

Herbal Drugs

Allium Sativum

Garlic has become a popular name used for a disease world, with a variety of records of hypotensive activity in several diseases, including hyperlipidemia, coronary heart attack, high blood pressure, age-related vascular changes or atherosclerosis, ear pain, syndrome of chronic fatigue (CFS), and menstrual disruption, garlic (Ashraf et al., 2022). Allicin has beneficial healing effects, and garlic odor is the primary active compound attribute. Garlic is considered a strong inhibitor of platelet aggregation. By stimulating the development of the relaxing factor derived from endothelium (EDRF), lower blood pressure causes muscles' smooth relaxation, and vasodilation is expected to be induced. For many diverse applications, such as decreasing the number of risks related to cardiovascular disease and hypertension (1) lowering cholesterol and LDL, (2) lowering HSD cholesterol, (3) lowering blood pressure, (5) enhancing blood circulation, (7) raising platelet inhibited aggregation and (8) decreased plasma viscosity, It is used in a variety of fields including HBP and the reduction of cardiovascular risk factors (Sawal *et al.*, 2021; Sharma *et al.*, 2021). It is believed that the effect of blood pressure is caused by the opening of ion channels in the vascular smooth muscle membrane (CA) and affects hyperpolarization and causes vasodilation.

Uncaria Tomentosa

Several species with the cat's law common name are related to that plant. Different phytochemicals in Uncaria tomentosa aqueous extract have different heart and blood effects (Oogaki *et al.*, 2021). Rhinophilline, hirsutism and mitraphylline are alkaloids of this plant. Rhinophylline has also been an agent for platelet aggregation and thrombosis. Blood clots can be avoided and minimized in blood vessels, endothelial blood vessels can be expanded, peripherals of blood vessels increased, heart rate decreased, and cholesterol reduced (Deana *et al.*, 2022; Natarajan *et al.*, 2022; Villegas Vílchez *et al.*, 2022).

Various chemical compounds have enhanced body water loss a nd smooth muscle relaxation (Kolodziejczyk-Czepas *et al.*, 2021). All these results may be beneficial in reducing BP. It has also been suggested that Uncaria tomentosa water extract can

help prevent stroke, heart attacks and cardiovascular system disorders (due to reduced C-reactive protein levels).

Rauwolfia Serpentina

The common name of the plant is snakeroot. This plant is used to treat high blood pressure. The hypertensive plant is considered to be the most effective. Hypertension and other cardiovascular disease reserpine and other alkaloids (Jajra & Rao, 2019; AlShehri *et al.*, 2022). Alkaloid isolated of R. Serpentine is the first effective medicinal drug commonly used in HTN long-term care (Wahid *et al.*, 2020). The treatment of tachycardia and thyrotoxicosis was introduced in 1952 with HTP Serpasil as reserpine. The reserpine, dihydroergocristine and diuretic mixture is still in nature (Brinerdin, Crystepin).

Coleus Forskohlii

Common name Forskolin is used for medicine in ayurvedic. The Forskolin, an aspect of this plant, has been identified by the Indian Central Medication Research Institute. Forskolin is reported to reduce the effects of blood pressure and relax the arterial vascular smooth muscle (Cammalleri *et al.*, 2020). In research with isolated cardiac tissue, Forskolin- membrane-adenomyosis and cytoplasmic protein kinase cAMP.

Ginkgo (Ginkgo Biloba)

In the dementia diagnosis, including vascular, mixed dementia, and Alzheimer's, fruits and leaves from the ginkgo tree. Ginkgo leaf is also utilized for cerebral vascular insufficiency disorders, particularly for the elderly, including headaches, memory loss, dizziness, tinnitus, hearing disorders, and trouble mood (Jialiken et al., 2021). There is also orally consumed for ischemic stroke. Ginkgo was used to improve cognitive problems and sleep habits in patients with Chronic Fatigue Syndrome (CFS), depression, CFS, and eye diseases, such as male degree and glaucoma (Das et al., 2022). Flavonoids and glycosides are the main activity of plants. Ginkgo is marketed in combination or as a single herbal compound. Thrombosis, heart disorders; arteriosclerosis, and angina pectoris. The single herbal compound can be found in tablets. Ginkgo extract has a very strong vascular effect. Extracts from Ginkgo leaves can be found in both clinical and experimental data, and the deepseated medium and small artery regions, in particular, induce vasodilation and increase vascular blood flow (Arunima et al., 2021; Kauser et al., 2022).

Hawthorne (Crataegus oxycantha and Crataegus monogyna)

Hawthorne has commonly treated cardiovascular diseases in many societies. However, It consists of active constituents, including oligomeric proanthocyanidins (OPCs), flavonoids, amines, triterpene saponins, and catechins (Bass *et al.*, 2022). Hawthorne showed a lowering mild blood pressure response up to maximal four weeks results. Coronary blood vessels are dilated by herbs. Rat found proanthocyanidins while *in*

vitro study. It is extracted from the hawthorn's relaxed vascular tone (Shahrestani *et al.*, 2021).

European Mistletoe

Nowadays, European Mistletoe is favored in medicine because of its hypotensive activity and anticancer properties. Mistletoe is familiar with antispasmodic, tumor-inhibiting, hypotensive, thymus stimulating activity, cardiotonic, and vasodilatory. Its pharmacological outcome includes a hypotensive activity. This was considered during the alcohol extraction of mistletoe (Japanese and European). When executed on cats, European and Japanese mistletoe showed lower blood pressure (Majeed & Rehman, 2021). Similar hypotensive results of mistletoe were shown in other animal experimental studies reported by other researchers.

Nigella Sativa

Although various medicinal plants (Family Ranunculaceae) are considered important herbs for a wide spectrum of pharmacological potential, cardiovascular disorders are treated with essential oil of this herb having the antioxidant property that makes it useful for the treatment. Thymol, thymoquinone, thymohydroquinone, and dithymoquinone. Carvacrol, tanethole and 4- terpineol are active constituents of Nigella sativa (Shoaei-Hagh *et al.*, 2021; Burlaka, 2022). The hypotensive action of this herb is just because of its essential oil. The volatile oil in an animal study found potential to act as an antihypertensive agent. Nigella's antioxidant properties are confirmed by TLC (Thin layer chromatography).

Hibiscus Sabdariffa

In non-pharmacological treatment, Hibiscus-sabdariffa is one potential. The calyces' infusions used in folk medicine are effective for High Blood Pressure and other conditions. Many West African countries traditionally used Hibiscus sabdariffa (leaves, calyx, and corolla) for medicinal principles. The antihypertensive response of the Hibiscus sabdariffa plant has been studied variously. Calyx of HS antihypertensive effect was reported in a study. In Lagos, the same results were produced independently (Abdelmonem *et al.*, 2022; Sumantri *et al.*, 2022). Fall in induced hypertensive rates in blood pressure is due to the extracted water of the dry HS (herbaceous stem) calyx, and antihypertensive effects of extracted dry HS attributed to mediation.

Ephedra Sinica

Ephedra sinica, Ephedra intermedia or *Ephedra equisetina are* dry HS (herbaceous stem). For the treatment of asthma, traditional Chinese medicine is commonly Small doses of Ephedra sinica. Phenylproamine alkaloids are present in all three Ephedra. Ephedrine (55-78%) and pseudoephedrine (12-23%) are present in 1-ephedrine and d-pseudoephedrine. *E. Sinica* (Mushagalusa Kasali *et al.*, 2021; Yousefian *et al.*, 2022). Although *ephedra* herb is available in a variety for purchase,

having different formulas like weight loss formulas. Ephedrine is a recognized sympathomimetic agent with an epinephrine structure, which acts on both α and β -adrenergic receptors (Hong *et al.*, 2021). This relaxes bronchial muscles and induces anti-asthmatic activity through its β -adrenergic function. By the α -lagonist effect, it induces a myocardial stimulation. α agonistic effect of Ephedrine constricts blood vessels, resulting in increased heart rate and BP (Blood Pressure) with rising cardiac output. Cerebral accidents and myocardial infarcts severe reactions are associated with *Ephedra herb*. This herb may be useful for lowering blood pressure medications.

Conclusion

For primary health care in developing countries, 80% use herbal medicines. Natural products are considered the best primary health care because of lesser side effects, safety, better cultural acceptability and inexpensiveness. Diet, exercise, and stress are the changes made in our lifestyle that can help lower BP (blood pressure). The most studied and widely used for hypertension are Allium Sativum, Uncaria tomentosa, Rauwolfia serpentina, and Coleus forskohlii. Ginkgo, Hawthorne, European Mistletoe, Nigella sativa, Hibiscus sabdariffa, and Ephedra sinica. Herbal medicine is studied as a potential therapeutic agent in treating hypertension.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

References

- Abdelmonem, M., Ebada, M. A., Diab, S., Ahmed, M. M., Zaazouee, M. S., Essa, T. M., ElBaz, Z. S., Ghaith, H. S., Abdella, W. S., Ebada, M., et al. (2022). Efficacy of Hibiscus sabdariffa on Reducing Blood Pressure in Patients With Mild-to-Moderate Hypertension: A Systematic Review and Meta-Analysis of Published Randomized Controlled Trials. Journal of Cardiovascular Pharmacology, 79(1), e64-e74.
- Agrawal, M., Nandini, D., Sharma, V., & Chauhan, N. S. (2010). Herbal remedies for treatment of hypertension. International Journal of Pharmaceutical Sciences and Research, 1(5), 1-21.
- Ahmad, A., Riaz, S., Nadeem, M. S., Mubeen, U., & Maham, K. (2022). Role of Carotenoids in Cardiovascular Disease. In *Carotenoids-New Perspectives and Application*. IntechOpen.
- Ajay, M., Chai, H. J., Mustafa, A. M., Gilani, A. H., & Mustafa, M. R. (2007). Mechanisms of the anti-hypertensive effect of Hibiscus sabdariffa L. calyces. *Journal of ethnopharmacology*, 109(3), 388-393.
- Akbarpour, S., Khalili, D., Zeraati, H., Mansournia, M. A., Ramezankhani, A., & Fotouhi, A. (2018). Healthy lifestyle

behaviors and control of hypertension among adult hypertensive patients. *Scientific Reports*, 8(1), 1-9.

- Alhazmi, R. A., Khayat, S. K., Albakri, M. H., Alruwaili, W. S., Bayazed, H. A., Almubarak, S. A., Albahrani, A. A., Alshahrani, A. A., Alharkan, A. A., Alreqei, H. M., et al. (2022). An overview on the assessment and management of polycystic ovarian syndrome. *World Journal of Environmental Biosciences*, 11(1), 17-23. doi:10.51847/Yaaa2745ZY
- AlHumaidi, M. A., AlJahdali, S. L., AlGab, M. K. M., AlRizqi, A. A., AlShammeri, A. N., & AlQarni, A. A. (2022). A surveybased study on dentists' knowledge and practices regarding lasers in Riyadh City. *Annals Journal of Dental and Medical Assisting*, 2(1), 8-13. doi:10.51847/E6TbI0HfXU
- Alotiby, A. A., & Al-Harbi, L. N. (2021). Prevalence of using herbs and natural products as a protective measure during the COVID-19 pandemic among the Saudi population: an online cross-sectional survey. Saudi Pharmaceutical Journal, 29(5), 410-417.
- AlShehri, O. M., Jali, N. M., Almutairi, Y. M., Aljrais, M. M., Alsirhani, A. M., & AlQudairi, A. S. (2022). Common causes of cusp fracture in adults; a systematic review. *Annals of Dental Specialty*, 10(2), 35-38. doi:10.51847/jBTdUqt7Cx
- Artru, F., Moschouri, E., & Denys, A. (2022). Direct intrahepatic portocaval shunt (DIPS) or transjugular transcaval intrahepatic portosystemic shunt (TTIPS) to treat complications of portal hypertension: indications, beyond Budd-Chiari technique, and outcomes syndrome. Clinics and Research in Hepatology and Gastroenterology, 101858.
- Arunima, C., Julia, J., & Prasobh, G. (2021). A review on role of ginkgo biloba in treating alzheimer's disease.
- Ashraf, R., Sarwar, M., Kamil, N., Wahid, S., & Qureshi, A. (2022). Analysis of dose and duration dependent effects of Allium sativum Linn and other hypocholesterolemic agents exhibited on dyslipidemia in patients with essential hypertension. *Pakistan Journal of Pharmaceutical Sciences*, 35(3).
- Aspite, S., Schepis, F., Roccarina, D., Gitto, S., Citone, M., Di Bonaventura, C., Bianchini, M., Arena, U., Vannucchi, A. M., Guglielmelli, P., et al. (2022). Portosystemic shunt is an effective treatment for complications of portal hypertension in hepatic myeloid metaplasia and improves nutritional status. *Liver International*, 42(2), 419-424.
- Baharvand-Ahmadi, B., & Asadi-Samani, M. (2017). A minireview on the most important effective medicinal plants to treat hypertension in ethnobotanical evidence of Iran. *Journal of Nephropharmacology*, 6(1), 3.
- Bailey, B., Euser, A. G., Bol, K. A., Julian, C. G., & Moore, L. G. (2022). High-altitude residence alters blood-pressure course and increases hypertensive disorders of pregnancy. *The Journal of Maternal-Fetal & Neonatal Medicine*, 35(7), 1264-1271.
- Bass, L. M., Ye, W., Hawthorne, K., Leung, D. H., Murray, K. F., Molleston, J. P., Romero, R., Karpen, S., Rosenthal, P., Loomes, K. M., et al. (2022). Risk of variceal hemorrhage

and pretransplant mortality in children with biliary atresia. *Hepatology*.

- Bell, C. S., Samuel, J. P., & Samuels, J. A. (2019). Prevalence of hypertension in children: applying the new American Academy of Pediatrics clinical practice guideline. *Hypertension*, 73(1), 148-152.
- Boa Sorte Silva, N. C., Petrella, A. F., Christopher, N., Marriott, C. F., Gill, D. P., Owen, A. M., & Petrella, R. J. (2021). The benefits of high-intensity interval training on cognition and blood pressure in older adults with hypertension and subjective cognitive decline: Results from the heart & mind study. *Frontiers in Aging Neuroscience*.
- Burlaka, I. (2022). Approach to correction of apoptotic disorders in children with early diabetic nephropathy. *Journal of Advanced Pharmacy Education and Research*, 12(2), 104-109. doi:10.51847/G6i3231Jnm
- Cammalleri, M., Dal Monte, M., Amato, R., Bagnoli, P., & Rusciano, D. (2020). A dietary combination of forskolin with homotaurine, spearmint and B vitamins protects injured retinal ganglion cells in a rodent model of hypertensive glaucoma. *Nutrients*, 12(4), 1189.
- Chang, W. T., Dao, J., & Shao, Z. H. (2005). Hawthorn: potential roles in cardiovascular disease. *The American Journal of Chinese Medicine*, 33(01), 1-10.
- Chia, Y. C. (2022). Hypertension in the Elderly: Pathophysiology and Clinical Significance. In *Hypertension and Cardiovascular Disease in Asia* (pp. 239-256). Springer, Cham.
- DalBó, S., & de Aguiar Amaral, P. (2017). Medicinal plants that can cause changes in blood pressure and interactions with antihypertensive agents. *American Journal of Ethnomedicine*, 4(1), 2-8.
- Das, R., Lami, M. S., Chakraborty, A. J., Mitra, S., Tallei, T. E., Idroes, R., Mohamed, A. A. R., Hossain, M., Dhama, K., Mostafa-Hedeab, G., et al. (2022). Ginkgo biloba: A Treasure of Functional Phytochemicals with Multimedicinal Applications. *Evidence-Based Complementary and Alternative Medicine*, 2022.
- Deana, N. F., Seiffert, A., Aravena-Rivas, Y., Alonso-Coello, P., Muñoz-Millán, P., Espinoza-Espinoza, G., Pineda, P., & Zaror, C. (2022). Review of available studies and guidelines in the field of prevention of COVID-19 infection in dental centers. *Annals Journal of Dental and Medical Assisting*, 2(1), 1-7. doi:10.51847/4VxEtFTh77
- Denisova, A. R., Solntseva, T. D., Zarmanbetova, A. S., Tkacheva, A. A., Sivakova, O. A., & Chazova, I. E. (2022). The incidence of cardiovascular and cerebrovascular complications in patients with uncontrolled hypertension. *Terapevticheskii arkhiv*, 94(1), 94-99.
- Dhingra, V., Dhingra, S., & Singla, A. (2013). Forensic and pharmacognostic studies of the Terminalia arjuna Bark. *Egyptian Journal of Forensic Sciences*, 3(1), 15-19.
- Diop, M., Niang-Diop, F., Dieng, S. D., Samb, A., Manga, G. E. D., Sané, A. P., Sène, M. B., Sambou, B., Goudiaby, A., & Diatta, E. A. (2022). Ethnobotanical study of medicinal plants for treatment of diabetes and hypertension used in communities near Fathala Forest, Senegal. *Ethnobotany Research and Applications*, 23, 1-15.

- Durazzo, A., Lucarini, M., Souto, E. B., Cicala, C., Caiazzo, E., Izzo, A. A., Novellino, E., & Santini, A. (2019). Polyphenols: A concise overview on the chemistry, occurrence, and human health. *Phytotherapy Research*, 33(9), 2221-2243.
- Ekblad, M. O., Gissler, M., & Korhonen, P. E. (2022). New theory about the pathophysiology of preeclampsia derived from the paradox of positive effects of maternal smoking. *Journal of Hypertension*, 40(6), 1223-1230.
- Fuchs, F. D., & Whelton, P. K. (2020). High blood pressure and cardiovascular disease. *Hypertension*, 75(2), 285-292.
- Giles, T. D., Sander, G. E., & Fernandez, C. (2018). Iatrogenicity of Blood Pressure measurement in the Diagnosis of Hypertension. *Iatrogenicity: Causes and Consequences of Iatrogenesis in Cardiovascular Medicine*, 28(29), 30.
- Gupta, H., Vidhale, T., Pustake, M., Gandhi, C., & Roy, T. (2022). Utility of ambulatory blood pressure monitoring in detection of masked hypertension and risk of hypertension mediated organ damage in normotensive patients with type 2 diabetes mellitus. *Blood Pressure*, 31(1), 50-57.
- Hong, M. H., Kim, H. Y., Jang, Y. J., Na, S. W., Han, B. H., Yoon, J. J., Seo, C. S., Lee, H. S., Lee, Y. J., & Kang, D. G. (2021). New Therapeutic Insight into the Effect of Ma Huang Tang on Blood Pressure and Renal Dysfunction in the L-NAME-Induced Hypertension. *Evidence-Based Complementary* and Alternative Medicine, 2021.
- Ike, N. A. (2020). Overview of the Phytochemicals of medicinal plants to lower blood pressure. *Scholars Academic Journal* of Pharmacy, 9(11), 318-329.
- Jagtap, M., Chandola, H. M., & Ravishankar, B. (2011). Clinical efficacy of Coleus forskohlii (Willd.) Briq.(Makandi) in hypertension of geriatric population. *Ayu*, 32(1), 59.
- Jajra, S. D., & Rao, S. (2019). Role of Rauwolfia Serpentina in the management of hypertension.
- Jennings, J. R., Muldoon, M. F., Allen, B., Ginty, A. T., & Gianaros, P. J. (2021). Cerebrovascular function in hypertension: Does high blood pressure make you old? *Psychophysiology*, 58(7), e13654.
- Jialiken, D., Qian, L., Ren, S., Wu, L., Xu, J., & Zou, C. (2021). Combined therapy of hypertensive nephropathy with ginkgo leaf extract and dipyridamole injection and antihypertensive drugs: A systematic review and metaanalysis. *Medicine*, 100(19).
- Kauser, S., Morrissey, H., & Ball, P. (2022). England local community pharmacists opinions on independent prescribing training. *Journal of Advanced Pharmacy Education and Research*, *12*(1), 30-37. doi:10.51847/PaNZ94aVtA
- Khattulanuar, F. S., Sekar, M., Fuloria, S., Gan, S. H., Rani, N. N. I. M., Ravi, S., Chidambaram, K., Begum, M. Y., Azad, A. K., Jeyabalan, S., et al. (2022). Tilianin: A Potential Natural Lead Molecule for New Drug Design and Development for the Treatment of Cardiovascular Disorders. *Molecules*, 27(3), 673.
- Kolodziejczyk-Czepas, J., Ponczek, M., Sady-Janczak, M., Pilarski, R., & Bukowska, B. (2021). Extracts from Uncaria tomentosa as antiplatelet agents and thrombin inhibitors-the

in vitro and in silico study. Journal of Ethnopharmacology, 267, 113494.

- Kushwaha, S., Betsy, A., & Chawla, P. (2012). Effect of Ashwagandha (Withania somnifera) root powder supplementation in treatment of hypertension. *Studies on Ethno-Medicine*, 6(2), 111-115.
- Liu, K., Luo, M., & Wei, S. (2019). The bioprotective effects of polyphenols on metabolic syndrome against oxidative stress: Evidences and perspectives. Oxidative Medicine and Cellular Longevity, 2019.
- Lopez, E. O., Ballard, B. D., & Jan, A. (2021). Cardiovascular disease. In *StatPearls [Internet]*. StatPearls Publishing.
- Maaliki, D., Shaito, A. A., Pintus, G., El-Yazbi, A., & Eid, A. H. (2019). Flavonoids in hypertension: a brief review of the underlying mechanisms. *Current Opinion in Pharmacology*, 45, 57-65.
- Majeed, M., & Rehman, R. U. (2021). Phytochemistry, Pharmacology, and Toxicity of an Epiphytic Medicinal Shrub Viscum album L.(White Berry Mistletoe). *Medicinal* and Aromatic Plants, 287-301.
- Martinez-Ríos, E., Montesinos, L., Alfaro-Ponce, M., & Pecchia, L. (2021). A review of machine learning in hypertension detection and blood pressure estimation based on clinical and physiological data. *Biomedical Signal Processing and Control*, 68, 102813.
- Mills, K. T., Stefanescu, A., & He, J. (2020). The global epidemiology of hypertension. *Nature Reviews Nephrology*, 16(4), 223-237.
- Mohsen Ibrahim, M. (2018). Hypertension in developing countries: a major challenge for the future. *Current Hypertension Reports*, 20(5), 1-10.
- Mondal, S., & Rahaman, S. T. (2020). Flavonoids: A vital resource in healthcare and medicine. *Pharmacy & Pharmacology International Journal*, 8(2), 91-104.
- Mumtaz, A., Ashfaq, U. A., ul Qamar, M. T., Anwar, F., Gulzar, F., Ali, M. A., Saari, N., & Pervez, M. T. (2017). MPD3: a useful medicinal plants database for drug designing. *Natural Product Research*, 31(11), 1228-1236.
- Mushagalusa Kasali, F., Ahadi Irenge, C., Murhula Hamuli, P., Birindwa Mulashe, P., Murhula Katabana, D., Mangambu Mokoso, J. D. D., Mpiana, P. T., & Ntokamunda Kadima, J. (2021). Ethnopharmacological Survey on Treatment of Hypertension by Traditional Healers in Bukavu City, DR Congo. Evidence-Based Complementary and Alternative Medicine, 2021.
- Nagar, H., Kang, S. K., Choi, S. W., Song, H. J., Choi, S. J., Piao, S., Kim, S., Lee, I., & Kim, C. S. (2020). Antihypertensive Effects of Rg3-Enriched Korean Vitamin Ginseng in Spontaneously Hypertensive Rats. *Natural Product Communications*, 15(1), 1934578X19900712.
- Nassiri-Asl, M., & Hosseinzadeh, H. (2016). Review of the pharmacological effects of Vitis vinifera (Grape) and its bioactive constituents: an update. *Phytotherapy Research*, 30(9), 1392-1403.
- Natarajan, G. P., Venkataraman, S. M., Pitchamuthu, S., & Rengaraj, M. (2022). Impact of Silicon Seed Priming on Osmoregulants, Antioxidants, and Seedling Growth of Maize Grown under Chemo-Stress. World Journal of

Environmental Biosciences, 11(2), 1-7. doi:10.51847/ODzSUPDgnz

- Nisha, J., Anbu, N., & Purushothaman, I. (2017). A Review on traditional herbs used in Parkinson's disease (Nadukku Vatham).
- Nowbar, A. N., Gitto, M., Howard, J. P., Francis, D. P., & Al-Lamee, R. (2019). Mortality from ischemic heart disease: Analysis of data from the World Health Organization and coronary artery disease risk factors from NCD Risk Factor Collaboration. *Circulation: Cardiovascular Quality and Outcomes*, 12(6), e005375.
- Oates, J. A. (2001). Antihypertensive agents and the drug therapy of hypertension. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*.
- Ofem, O. E., Eno, A. E., Imoru, J., Nkanu, E., Unoh, F., & Ibu, J. O. (2007). Effect of crude aqueous leaf extract of Viscum album (mistletoe) in hypertensive rats. *Indian Journal of Pharmacology*, 39(1), 15.
- Oliva, R. V. (2019). A review on the status of hypertension in six Southeast Asian Countries. *Hypertension*, *5*(2), 45-48.
- Oogaki, Y., Ozawa, R., Seshima, K., Shinoda, R., Torii, Y., Takahashi, H., Iwata, H., Kuwayama, T., & Shirasuna, K. (2021). Uncaria tomentosa extract (AC-11) improves pregnancy hypertension together with suppression of sFlt-1 and sEng. *Pregnancy Hypertension*, 26, 127-132.
- Qayyum, R., Qamar, H. M. U. D., Khan, S., Salma, U., Khan, T., & Shah, A. J. (2016). Mechanisms underlying the antihypertensive properties of Urtica dioica. *Journal of Translational Medicine*, 14(1), 1-13.
- Roerecke, M., Kaczorowski, J., & Myers, M. G. (2019). Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension: a systematic review and meta-analysis. *JAMA Internal Medicine*, 179(3), 351-362.
- Sawal, S. B., Thakre, M. P., & Ganeshrao, P. (2021). Review on effect of garlic (Allium Sativum) on blood pressure.
- Shahrestani, S., Hitos, K., Hort, A., Spike, E., Gibbons, T. J., Lendzion, R., Yuen, L., Pleass, H. C., & Hawthorne, W. J. (2021, January). Successful Expectant Management of Nonocclusive Thrombosis in Simultaneous Pancreas-Kidney Transplantation. In *Transplantation Proceedings* (Vol. 53, No. 1, pp. 371-378). Elsevier.
- Shaikh, J. R., & Patil, M. K. (2020). Qualitative tests for preliminary phytochemical screening: An overview. *International Journal of Chemical Studies*, 8(2), 603-608.
- Sharma, N., Behl, T., Singh, S., Bansal, A., Singh, S. K., & Zahoor, I. (2021). Expatiating the therapeutic profile of garlic (Allium sativum): A bench to bedside approach. *Biointerface Research in Applied Chemistry*, 11(6), 14225-14239.
- Shoaei-Hagh, P., Kamelan Kafi, F., Najafi, S., Zamanzadeh, M., Heidari Bakavoli, A., Ramezani, J., Soltanian, S., Asili, J., Hosseinzadeh, H., Eslami, S., et al. (2021). A randomized, double-blind, placebo-controlled, clinical trial to evaluate the benefits of Nigella sativa seeds oil in reducing

cardiovascular risks in hypertensive patients. *Phytotherapy Research*, 35(8), 4388-4400.

- Shrout, T., Rudy, D. W., & Piascik, M. T. (2017). Hypertension update, JNC8 and beyond. *Current Opinion in Pharmacology*, 33, 41-46.
- Sumantri, A. F., Bashari, M. H., Tadjoedin, H., & Atik, N. (2022). Risk of coronavirus disease 2019 (COVID-19) infection on leukemia patients: basic science to clinical aspect. *Journal* of Advanced Pharmacy Education and Research, 12(1), 38-45. doi:10.51847/qqIktBAHB7
- Surma, S., Romańczyk, M., Witalińska-Łabuzek, J., Czerniuk, M. R., Łabuzek, K., & Filipiak, K. J. (2021). Periodontitis, blood pressure, and the risk and control of arterial hypertension: epidemiological, clinical, and pathophysiological aspects—review of the literature and clinical trials. *Current Hypertension Reports*, 23(5), 1-14.
- Tanaka, M. (2020). Improving obesity and blood pressure. *Hypertension Research*, 43(2), 79-89.
- Thomas, A., Proust-Lima, C., Baillet, M., Helmer, C., Delcourt, C., Foubert-Samier, A., Catheline, G., Féart, C., & Samieri, C. (2021). Plasma carotenoids and medial temporal lobe atrophy in older adults. *Clinical Nutrition*, 40(4), 2460-2463.
- Toh, D. W. K., Sutanto, C. N., Loh, W. W., Lee, W. Y., Yao, Y., Ong, C. N., & Kim, J. E. (2021). Skin carotenoids status as a potential surrogate marker for cardiovascular disease risk determination in middle-aged and older adults. *Nutrition, Metabolism and Cardiovascular Diseases*, 31(2), 592-601.
- Vaz, N. P., De Oliveira, D. R., Abouelella, G. A., & Khater, H. F. (2018). The black seed, Nigella sativa (Ranunculaceae), for prevention and treatment of hypertension. JN Govil and Bhardwaj N, 48, 221-244.
- Villegas Vílchez, L. F., Ascencios, J. H., & Dooley, T. P. (2022). GlucoMedix®, an extract of Stevia rebaudiana and Uncaria tomentosa, reduces hyperglycemia, hyperlipidemia, and hypertension in rat models without toxicity: a treatment for

metabolic syndrome. *BMC Complementary Medicine and Therapies*, 22(1), 1-19.

- Villegas, L. R., & Le, M. T. (2019). Compositions and methods for preventing or treating pulmonary hypertension, Google Patents.
- Wahid, M. A., Khalid, M., Hasan, K. A., Roqaiya, M., & Fatima, H. (2020). Potential Role of Unani Herbs in Management of Hypertensive Cardiomyopathy: A Review. *Research & Reviews: A Journal of Unani, Siddha and Homeopathy*, 7(1), 1-6.
- Waśkiewicz, A., Zujko, M. E., Szcześniewska, D., Tykarski, A., Kwaśniewska, M., Drygas, W., & Witkowska, A. M. (2019).
 Polyphenols and dietary antioxidant potential, and their relationship with arterial hypertension: A cross-sectional study of the adult population in Poland (WOBASZ II). Advances in Clinical and Experimental Medicine, 28(6).
- Webb, A. J., & Werring, D. J. (2022). New insights into cerebrovascular pathophysiology and hypertension. *Stroke*, 53(4), 1054-1064.
- Xiang, L., Li, Y., Deng, X., Kosanovic, D., Schermuly, R. T., & Li, X. (2018). Natural plant products in treatment of pulmonary arterial hypertension. *Pulmonary Circulation*, 8(3), 2045894018784033.
- Yang, P. (2019). Medication and application for treatment of hypertension based on anion and traditional Chinese medicine, 2019, Google Patents.
- Yousefian, M., Ghazi, A., Amani, F., & Movaffagh, B. (2022). Mortality rate in patients admitted to the ICU based on LODS, APACHE IV, TRIOS, SAPS II. Journal of Advanced Pharmacy Education and Research, 12(1), 56-62. doi:10.51847/CgHzosuz9x
- Zheng, W., Wang, Z., Jiang, X., Zhao, Q., & Shen, J. (2020). Targeted drugs for treatment of pulmonary arterial hypertension: past, present, and future perspectives. *Journal* of Medicinal Chemistry, 63(24), 15153-15186.