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# POTENTIAL OF HERBAL PLANTS AS ANTIHYPERTENSIVE THERAPY: A REVIEW

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### ABSTRACT

**Background:** Hypertension has become a significant health problem in the world which the sufferer increases every year. Herbal treatment for lowering blood pressure that has been widely used in many countries shows the potential as an anti-hypertensive. This study aims to provide an overview of the herbs that have the effect of lowering blood pressures as the treatment of hypertension.

**Methods:** This study used a systematic review based on the PRISMA (Preferred Reporting Items for Systematic Reviews & Meta-Analyses) protocol as a writing guideline. Electronic databases used in this study were Science Direct, PubMed, and Google Scholar. Only articles using interventions research design and containing full text both in English and Indonesian language were included in this study.

**Results:** Of 207 articles recorded in the searching literature, only fourteen articles were included in this study. Study found that herbs which had the effect as antihypertensive therapy were *Apium graveolens*, *Allium sativum*, *Centella asiatica*, *Orthosiphon stamineus benth*, *Beta vulgaris*, and *Vitis vinifera*. The main components of those herbs consisted of *n*-butylphthalide, apigenin, potassium, flavonoids, triterpenoid, polysulfide, sinensetin, nitrate, and polyphenols.

**Conclusions:** Many herbal plants found potentially lowering the blood pressures and considered as complementary treatment without any side effects. Further research is still needed on the effects of herbs in lowering the blood pressure to the human subject and its reversible effects, as well as the safety of herbs to human health when it is used for a long time.

**Keywords:** Herbs, blood pressure, antihypertensive therapy

### INTRODUCTION

Hypertension has become a major health problem world in which the sufferer is increasing every year [1]. Moreover, it is often called the silent killer because it is a chronic disorder without symptoms quietly damage the blood vessels, heart, brain, and kidneys if undetected and untreated. Also, an increase in blood pressure is also a risk factor for coronary heart disease which has been the cause of death in many countries [2].

According to the World Health Organization, the overall prevalence of hypertension in 2000 was approximately 26.4%. The world's population with hypertension will increase by 60% to approximately 1.56 billion in 2025 [3]. Based on data Riskesdas 2018, the prevalence of hypertension in Indonesia is 34.1%, this shows the incidence of hypertension has increased compared with the previous year in 2013 the prevalence of hypertension in Indonesia by 25.8% [4].

According to Zhang et al. 2015 study, a linear relationship between blood pressure and risk of cardiovascular events has been identified that hypertension is a major risk factor for cardiovascular disease (CVD)[5]. Epidemiological studies have shown a close relationship between the decrease in blood pressure and cardiovascular risk, suggesting that the reduction of high systolic blood pressure

(mmHg SBP.140) of 20 mm Hg or higher diastolic blood pressure reductions (DBP.90 mmHg) of 10 mmHg is associated with a reduction in risk 50% of cardiovascular disease [6].

Treatment of hypertension can be administered pharmacological and non-pharmacological; non-pharmacological treatment is using herbal or traditional materials (CAM). Efforts to improve the safety and efficacy of traditional medicine is also supported by the WHO; this is because the side effects of the use of traditional medicine are relatively less compared to modern medicine[7]. Side effects of pharmacological drugs usually cause discontinuation of therapy in many conditions, including hypertension [8].

Herbal-based traditional medicine has developed rapidly and used in different countries; the WHO supports the utilization of herbal medicine as a potential therapeutic strategy [9]. According to the WHO, the use of herbal medicine around the world in more than two to three times that of conventional drugs, herbal remedies from plants have existed since human civilization and also much used as a primary ingredient of modern medicine[10]. This is also evidenced by the high interest in complementary medicine and nutrition has increased, including those with cardiovascular conditions, regularly use complementary therapies [6].

Indonesia has a lot of native medicinal plants that have been used to treat ailments for centuries. Among these plants, herbs, a word from the Javanese language, subject to the traditional herbal medicine [11]. At present, potential herbal medicine formula famous anti-hypertensive, which contain celery (*Apium graveolens*) and leaves the cat's whiskers (*Orthosiphon Stamineus Benth*) has been used for many years after was designed as a new phytopharmacy [9]. Additionally, other anti-hypertensive herbs, leaf Gotu kola (*Centella Asiatica*), also used to treat hypertension [12][13]. Nitrate content in beetroot (*Beta vulgaris*) [14]. Polyphenolic compounds contained in grape (*Vitis vinifera*) is also potentially in decreasing blood pressure and can be used as antihypertensive therapy [3].

The purpose of this study is to identify and analyze several types of herbs that have the potential to lower blood pressure as the treatment of hypertension. Hopefully, the information can be developed and applied by the community.

## METHODS

This study used literature review based on the PRISMA (Preferred Reporting Items For Systematic Reviews & Meta-Analyses).

### *Search Strategy and Data Sources*

Literature search in this study was conducted through a Science Direct database search, PubMed, and Google Scholar. The keywords used include "herbs," "blood pressure," "hypertension," and "herbs for hypertension". The range of publications used is from January 2011 to January 2019 which discuss herbs and blood pressure.

### *Eligibility Criteria*

The inclusion criteria in this study were as follows: research available full text, type of experimental studies, articles in Indonesian or English, study interventions herbs against hypertension, year of publication starting from 2011 onwards. The exclusion criteria in this study were an editorial, review, articles and not the full text, research in addition to the experimental design, the article are not Indonesian and English.

### *Data Extraction*

Research article search was conducted from January 2011 to February 2019. Authors independently conducted article selection and data extraction. After the search of the published articles, the filters options of the databases were used to meet the inclusion criteria. Selected references were filtered by screening the title, abstract, or full-text publication to identify studies that include relevance to serve as a reference. We also looked at the contents of the articles to easily categorize the factors that affect the

effectiveness of herbs in decreasing blood pressure. The data were obtained and analyzed from the selected articles.

## RESULTS

In the early stages of the search articles through the ScienceDirect database, PubMed and Google Scholar obtained a total of 207 articles.

Furthermore, selecting the same article (duplicate article) published on ScienceDirect, PubMed and Google Scholar, the remaining 158 articles. Of these 78 articles obtained are deemed relevant. Then, screening based on abstracts of studies with consideration of articles in Indonesian or English, not the kind of experimental research, not in the form of a thesis or a thesis, and research of herbal interventions not against hypertension, then selected 14 articles to be analyzed. Articles used as samples are further identified and presented in the following figure 1

There are many herbs that have the potential to lower blood pressure. Of the fourteen articles included, four were discussed about celery (*Apium graveolens*), Two about Gotu Kola (*Centella Asiatica*) three about garlic (*Allium sativum*), three about beet (*Beta Vulgaris*), 2 about wine (*Vitis vinifera*) and one about cat whiskers (*Orthosiphon Stamineus Benth*). All studies were conducted between 2012 and 2019 (Table 1). Different parts of herbal were administered in the studies. The parts used in celery were seed and leaf Gotu Kola and Cat whiskers also used leaf part for the treatment, Meanwhile the parts used in Beet were fruit and Intact parts for Garlic. Fruit and Skin Parts of Wine also had been used for the treatment.

The result showed that celery seed extract was effective in lowering systolic blood pressure (SBP) of 4.6 mmHg and diastolic blood pressure (DBP) 4.5 mmHg at week 3. It was also effective in lowering blood pressure in hypertensive rats but did not affect normotensive rats. Water boiled celery have a significant effect in reducing systolic and diastolic blood pressure in hypertensive patients, with a significance value of  $p < 0.05$ .

Extracts of *Centella Asiatica* (16g / 20ml / kg) significantly decreased the arterial blood pressure, systolic, and diastolic elevated with N-nitro-L-arginine methyl ester (L-NAME) induced in hypertensive rats, was observed within 90 minutes. The content of triterpenoids in chloroform fraction C. asiatica shows antihypertensive effects on phenylephrine-induced hypertensive rats.

Garlic supplementation showed a significant reduction in systolic and diastolic blood pressure. Dietary garlic homogenates showed a significant reduction of systolic blood pressure (between 6.6 and 7.5 mmHg) and diastolic BP (between 4.6 and 5.2 mmHg) compared to placebo after 8 and 12 weeks of treatment.

Extraction of water (WOS), the methanol extract (WMOS) of *Orthosiphon Stamineus Benth* (1: 1), increase the antihypertensive effect by reducing vasoconstriction through changes  $\alpha$ 1-adrenergic receptor activity and AT1 after administered orally for 14 days in male rats with hypertension.

BJ consumption significantly, and in a way that depends on the dose near, lower systolic blood pressure (SBP, P, 0, 01) and diastolic blood pressure (DBP, P, 0, 001) for 24 hours. The bread containing 100g beetroot red or white lower systolic blood pressure and diastolic blood pressure for 24 hours, with no statistical differences between varieties, but the red beet more significant than the white beets.

Crude wine extract lowers arterial pressure, systolic and diastolic (MAP, SP, and DP) compared with the control group, at a dose of 125 mg/kg which is significantly greater than the control group ( $P < 0.05$ ). Grape skin extract 200 mg/kg/ vo given for 21 days to give the effect a decrease in systolic blood pressure in hypertensive male rats.

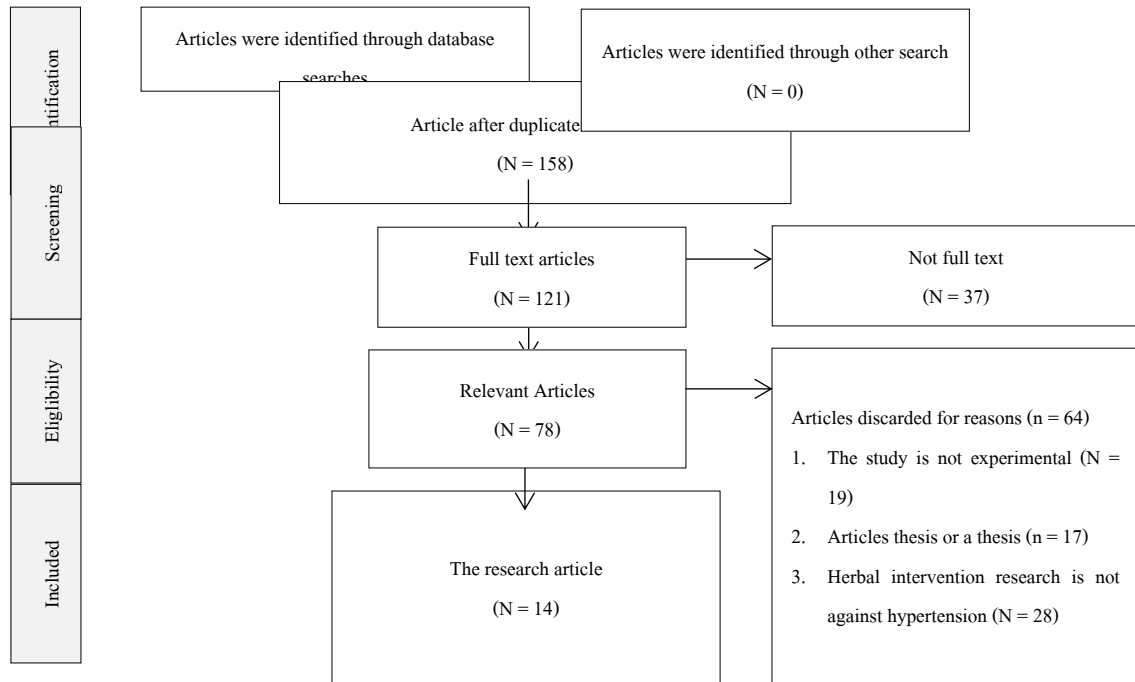


Figure 1. Schemes search results and selection of research articles

## DISCUSSION

Hypertension is a significant risk factor for morbidity and mortality worldwide. The main concern is that the treatment of hypertension in a large number of patients with hypertension are not satisfactory, and compliance with antihypertensive agents is usually bad [5], [26]. Today, the approach Complementary and Alternative Medicine (CAM) has been supported by clinical studies and meta-analyzes to lower blood pressure and increase the effects of symptoms [5]. Herbs are one way to lower blood pressure, or hypertension is a complementary treatment without any side effects [17].

Bad lifestyle and low intake of fruits and vegetables can be becoming a risk factor for high blood pressure [14]. Therefore, increased consumption of fruits and vegetables can be a precaution against hypertension and cardiovascular disease. Epidemiological studies have shown certain food groups such as green leafy vegetables can prevent high blood pressure and also have the most significant protection against coronary heart disease and ischemic stroke risk [23].

*Apium graveolens* or celery, typically used in traditional medicine as an anti-hypertensive agent, contains chemical compounds such as apiin, apigenin, isoquercitrin, and sesquiterpene [16]. The content of apigenin acts as a calcium antagonist has a vasodilatory effect[1]. Besides celery contains n-butylphthalide (NBP) as one of the major factions, these are oily and colorless compounds in celery. The oily fraction of celery seeds play an important role in the antihypertensive effect of this herb. Some studies have reported that the NBP has a diuretic effect in rats. Thus, the effect of diuretic could be one possible mechanism of antihypertensive of celery seed [2]. Compounds 3-n-butylphthalide in celery can reduce the concentration of stress hormones so that the blood vessels re-dilate and relax the smooth muscle layer of blood vessels. The active compound apigenin can prevent the constriction of blood vessels, celery helps lower blood pressure thanks to the active compound apigenin-like calcium antagonists like contained in the hypertension drug which is very useful to prevent narrowing of the arteries and high blood pressure[27] [28].

Table 1. List of herbs used to treat hypertension

Studies	Year	Herbal name	Common Name (in Indonesia)	Parts used	Result	How / Form Usage
D. Madhavi, D. Kagan, et al. [15]	2013	<i>Apium graveolens</i>	Celery	Seed	Celery seed extract is effective in lowering systolic blood pressure (SBP) of 4.6 mmHg and diastolic blood pressure (DBP) 4.5 mmHg at week 3. After 6 weeks of consumption, a decrease in SBP and DBP compared to baseline, respectively 8.9 and 8.5 mmHg (P <0.005).	Extract
M. Mogadham, Imenshahidi M., et al. [2]	2013	<i>Apium graveolens</i>	Celery	Seed	Celery seed extracts effective in lowering blood pressure in hypertensive rats but did not affect normotensive rats. Provision of 300mg / kg extracts heksanik, methanol, and aqueous ethanol (20/80, v / v) of celery seeds led to a decrease in BP, 60, 25 and 23 mmHg in 38 and 24 beats.	Extract
S. Siska, Mun'im A., et al. [16]	2018	<i>Apium graveolens</i>	Celery	Seed	Oral administration celery extract increases Cmax (38.67%), T1 / 2 (37.84%) and AUC (58.10%) and decreased to (27.45%) of captopril in Group II (celery + captopril) compared with Group I (captopril). Celery extract may alter the pharmacokinetics of captopril when given in combination.	Extract
HS, Diamond EO, Junaid, et al. [17]	2017	<i>Apium graveolens</i>	Celery	Leaf	Water boiled celery have a significant effect in reducing systolic and diastolic blood pressure in hypertensive patients, with a significance value of p <0.05.	water boiled
Intharachatom T., R. Srisawat [18]	2013	<i>Centella Asiatica</i>	Gotu Kola / Gotu Kola	Leaf	Extracts of <i>Centella Asiatica</i> (16g / 20ml / kg) significantly decreased the arterial blood pressure, systolic, and diastolic elevated with N-nitro-L-arginine methyl ester (L-NAME) induced in hypertensive rats, was	Extract



Harwoko, Pramod S., et al. [12]	2014	<i>Centella Asiatica</i>	Gotu Kola / Gotu Kola	Leaf	observed within 90 minutes. The content of triterpenoids in chloroform fraction <i>C. asiatica</i> shows antihypertensive effects on phenylephrine-induced hypertensive rats.	Extract
Ried K., Frank O., et al [19]	2013	<i>Allium sativum</i>	Garlic	Intact	Capsules of garlic reduced systolic blood pressure an average significantly from $11.8 \pm 5.4$ mmHg for 12 weeks in groups of two capsules, and achieve a significant reduction in the limit of 4 capsules of garlic group at 8 weeks ( $7.4 \pm 4.1$ mm Hg, $P = 0.07$ ).	Extract
R. Ashraf, R. Khan, et al. [20]	2013	<i>Allium sativum</i>	Garlic	Intact	Garlic supplementation showed a significant reduction in systolic and diastolic blood pressure. In the treatment group garlic, decreased SBP and DBP were significantly ( $p < 0.005$ ) was observed when compared with atenolol and placebo.	Extract
Y. Nakasone, Y. Nakamura, et al [21]	2013	<i>Allium sativum</i>	Garlic	Intact	Dietary garlic homogenates showed a significant reduction of systolic blood pressure (between 6.6 and 7.5 mmHg) and diastolic BP (between 4.6 and 5.2 mmHg) compared to placebo after 8 and 12 weeks of treatment. Homogenate intake of garlic for 12 weeks did not cause problematic side effects clinically.	Dried garlic
N. Manshor, Dewa A., et al. [22]	2013	<i>Orthosiphon Stamineus Benth</i>	Cat Whiskers	Leaf	Extraction of water (WOS), the methanol extract (WMOS) of <i>Orthosiphon Stamineus Benth</i> (1: 1), increase the antihypertensive effect by reducing vasoconstriction through changes $\alpha$ 1-adrenergic receptor activity and AT1 after administered orally for 14 days in male rats with hypertension.	Extract

D. Hobbs, N. Kaffa, et al. [23]	2012	<i>beta Vulgaris</i>	beet	Fruit	BJ consumption significantly, and in a way that depends on the dose near, lower systolic blood pressure (SBP, P, 0, 01) and diastolic blood pressure (DBP, P, 0, 001) for 24 hours.	Juice
D. Hobbs, N. Kaffa, et al. [23]	2012	<i>beta Vulgaris</i>	beet	Fruit	The bread containing 100g beetroot red or white lower systolic blood pressure and diastolic blood pressure for 24 hours, with no statistical differences between varieties, but the red bit more significant than the white bits.	Bread
A.Jajja, A.Sutyarjoko, et al. [24]	2014	<i>beta Vulgaris</i>	beet	Fruit	The concentration of beet juice daily reduces systolic BP after 3 weeks ( $-7.3 \pm 5.9$ mm Hg, $P = 0.02$ ); However The effect was not sustained after cessation of supplementation (weeks 4, $2.8 \pm 6.1$ mmHg, $P = .09$ ). On the subject of overweight older, supplementation is effective in the reduction of beet juice daily systolic BP, although the effect was not significant when measured by 24-hour ABPM or clinic BP rest	Juice
M. Nematbakhsh, Eshragh F., et al [25]	2012	<i>Vitis vinifera</i>	Wine	Fruit	Crude wine extract lowers arterial pressure, systolic and diastolic (MAP, SP, and DP) compared with the control group, at a dose of 125 mg/kg which is significantly greater than the control group ( $P < 0.05$ ).	Extract
G. Bomfim, D. Musial, et al. [3]	2019	<i>Vitis vinifera</i>	Wine	Skin	Grape skin extract 200 mg/kg/ vo given for 21 days to give the effect a decrease in systolic blood pressure in hypertensive male rats	Extract

Siska et al (2018) evaluated the effects of celery on hypertension medication captopril showed that oral administration of extract of celery increase  $C_{max}$  (38.67%),  $T_{1/2}$  (37.84%) and AUC (58.10 %) and decreased to (27.45%) of captopril in Group II (celery + captopril) compared with Group I (captopril). Celery extract may alter the pharmacokinetics of captopril when given in combination. This combination could be used for initial treatment of hypertension, as well as an increase in plasma captopril, which can increase effectiveness [16].

The research result Diamondet al. (2017) also showed that the water decoction of celery significantly decreases systolic blood pressure and diastolic blood pressure. Potassium (potassium) contained in celery is beneficial to increase the intracellular fluid to the extracellular fluid draw so that a change in the balance of the sodium-potassium pump that will cause a drop in blood pressure. The significant difference between the blood pressure before and after the administration of celery cooking water, which is evident from the mean pre-test blood pressure of 172.27 mmHg systolic and diastolic amounted to 106.36 mmHg. Mean systolic blood pressure is the first day of 160.00 mmHg and diastolic by 91.82 mmHg. While mean blood pressure on the second day at 141.82 mmHg systolic and diastolic amounted to 90.45 mmHg [17].

*Centella Asiatica* or gotu kola leaf has the ability and has been found to lower blood pressure, thereby reducing hypertension [29]. *Centella Asiatica* contains higher total phenolic content contributed by flavonoids such as quercetin, kaempferol, catechins, rutin, apigenin and naringin which has a direct effect in lowering blood pressure. Flavonoids are found in the *Centella asiatica*, found to have a hypotensive effect in hypertensive rats induced by L-NAME and has been shown to improve cardiovascular smooth muscle relaxation (antihypertensive effect) [18]. In the study Harwoko, et al (2014) showed that the content of triterpenoids in chloroform fractions *C. asiatica* (CFCA) is more dominant than the flavonoid/phenolic. TLC-densitometric Data show that the content of asiaticoside CFCA is  $0.402 \pm 0.02\%$ . CFCA show antihypertensive effects on phenylephrine-induced hypertensive rats [12].

*Allium sativum* or Garlic is one of the effective herbal and safe for the management of hypertension [5]. Polysulfide derivative gasotransmitter garlic stimulates the production of H<sub>2</sub>S and increasing regulation of vascular endothelial nitric oxide (NO), which induces relaxation of smooth muscle cells, vasodilation, and a decrease in blood pressure [6]. Garlic reduces prostaglandin E<sub>2</sub> and thromboxane B<sub>2</sub> levels and thereby may reduce hypertension [30]. Supplementation organosulfur compound derived from garlic can overcome the shortage of sulfur which may play a role in the etiology of hypertension. In aged garlic extracts, containing S-allyl cysteine as bioactive sulfur compounds, in particular, can be standardized and very well tolerated, with little or no harmful interactions that are known when taken with BP-lowering drugs or other blood thinners [6]. Aged garlic extract has higher efficacy than other garlic preparations [19].

Antihypertensive properties of garlic linked to stimulation of intracellular nitric oxide, hydrogen sulfide, and blockage of the production of angiotensin II, which acts on vasodilation and thus has the potential to lower blood pressure [19]. Research Ashraf et al (2013) showed garlic extracts lower the SBP and DBP with significant results in the dose and duration of control compared with placebo and antihypertensive agents (Atenolol) on passing hypertension stage 1 at 12 weeks and 24 weeks [20]. In the research by Y. Nakasone et al (2013) describe the intake of garlic for 12 weeks did not cause problematic side effects clinically. Dietary garlic homogenates well tolerated, and has the effect of clinically relevant hypotension in adults with mild hypertension, but not in those with prehypertension [21].

*Orthosiphon Stamineus Benth* or cat (2013) whiskers have been used as a diuretic in some Southeast Asian countries, especially Indonesia. The diuretic activity caused by the presence of sinensetin that can lower blood pressure [1]. Leaf cat whiskers have become known as a traditional herbal medicine hypertension, research Manshor, et al (2013) demonstrated the extraction of clean water (WOS) the methanol extract (WMOS) of *Orthosiphon Stamineus Benth* (1: 1) increase the antihypertensive effect



by reducing vasoconstriction through changes in receptor activity  $\alpha_1$ - adrenergic and AT1 after administered orally for 14 days in male rats with hypertension. In WMOS, vasorelaxation increase may be because the vasodilator PGI2 continue to be released as shown by the tonic effect on platelet CAMP [22].

*Beta Vulgaris* or beet included as one of the vegetables that contain nitrates ( $\text{NO}_3^-$  is the highest [23]. Nitrate from beetroot that is concentrated in the saliva and is exposed on the dorsal tongue symbiotic bacteria transform inorganic  $\text{NO}_3^-$  into nitrite  $\text{NO}_2^-$  by bacterial nitrate reductase (i.e., xanthine oxidase). Saliva is rich in nitrogen compounds reaches the stomach where a small portion of  $\text{NO}_2^-$  is reduced to NO by non-enzymatic reactions. Nitric oxide (NO) is a molecule that is synthesized in the endothelium that can have a significant effect on the maintenance of vascular homeostasis, both with a strong dilatory effect, control systemic blood pressure, or delay atherogenesis[14]. Continuous production of NO by the endothelium plays an important role in the maintenance of vascular homeostasis; NO can be in the biosynthesis in vivo after ingestion of dietary nitrate inorganic nitrate from beetroot juice (BJ). Study D. Hobbs, et al (2012) demonstrated that systemic NO production increases with the decrease in BP after BJ consumption and bread enriched with beetroot [23]. Further studies conducted by Jajja, et al (2014) showed supplementation of beet juice three weeks caused a progressive decrease in systolic blood pressure daily intervention in subjects with older overweight, but the effect was not significant when measured by 24-hour ABPM blood pressure clinic or rest [24].

*Vitis vinifera* or wine in the traditional medicine of Iran is believed to control hypertension in raw grape juice dosage forms which are very similar to vinegar. Raw wine is rich in antioxidants of polyphenolic compounds. The existence of polyphenol compounds in wine plays a role in the cardiovascular system. In studies Nematbakhsh (2013) preparations in the form of raw grape extract in mice potentially weaken the arterial blood pressure, systolic blood pressure, and diastolic blood pressure through vasodilation induced by the production of nitric oxide. A decrease in blood pressure by raw grape extract may occur through inhibition of the RAS activity both by the effects of the angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor [25].

Further research Bomfim G. et al (2018) shows that grape skin extract (ACH09) provides an antihypertensive effect in diabetic rats (streptozotocin) and hypertensive (SHR), this effect is associated with increased cardiovascular functionality (atria and aorta) receptor-mediated primarily by purinergic. ACH09 extracts have an effect on systolic blood pressure drop significantly in animals with diabetes and hypertension[3], Polyphenols (30%) and malvidin-3-O-glucoside (3%) contained in the extract ACH09 have antihypertensive effects, mainly by inducing the functional improvement of transmission neurotin purinergic to modulate receptor purinergic, is responsible for the relaxation depends on the endothelium, and is responsible for the vasoconstrictor response. Supplementation of the diet with foods rich in polyphenolic compounds, one of which is contained in red wine potential in diet therapy for the treatment of hypertension, diabetes and other metabolic diseases [3].

## CONCLUSION

Herbal supplementation is one way to lower blood pressure, or hypertension is a complementary treatment without any side effects. There are various types of traditional plants such as, *Apium graveolens*, *Centella Asiatica*, *Allium sativum*, *Stamineus Orthosiphon Benth*, *Beta Vulgaris*, and *Vitis vinifera* formula that has been used as a potential anti-hypertensive. The main components of which have an antihypertensive effect in the herbs, among others n-butylphthalide, apigenin, potassium, flavonoids, triterpenoid, polysulfide, sinensetin, nNitrate, and polyphenols.

Further research is still needed on the effects of herbs with recent studies as well as potentially lower the blood pressure to the human subject, reversibility effects, and safety of herbs to health when used in a long time.

## CONFLICT OF INTEREST

Authors declare no conflict of interest in this research with companies, publishers, authors or earlier.

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