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Review article

Anti-hypertensive medicinal plants and their mode of action

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ABSTRACT

This review discusses the medicinal plants used in traditional medicine for the treatment of hypertension and their reported mode of action and efficacy. High blood pressure is considered a major risk factor for cardiovascular diseases (CVD) and strokes. Owing to its high prevalence and association with increased morbidity and mortality, it is a major worldwide health problem. According to the data of Global Health Observatory (GHO), in 2014 about 22% of adults aged 18 and above were reported with elevated blood pressure. Between 2010 and 2014 the mean systolic blood pressure of the world's population has stayed constant at 124 mmHg. Historically, a number of plants and their formulations have been in use for the treatment of hypertension. Awareness of plant based medications and therapeutics are continuously increasing worldwide, hence the acceptance and demand. However, very few of these have been validated scientifically through stringent in vivo animal studies and clinical trials. Most of the available scientific data confirming the antihypertensive potential of traditionally used plants lacks systematic studies on their mode of action, efficacy, stability, toxicity and safety. In-depth scientific validation studies are required to authenticate the traditional medications as alternative and complementary drugs for the treatment of hypertension.

Contents

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; ACE, Angiotensin converting enzyme; ECEs, ET converting enzymes; NO, Nitric Oxide; SHR, Spontaneously Hypertensive Rats; 2K1C, two-kidney one clip (2K1C).

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1. Introduction

In hypertension, the blood flows through the blood vessels with a higher force compared to normal conditions. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) below 120 mmHg and 80 mmHg respectively is defined as normal blood pressure. SBP of 120–139 mmHg or DBP 80–89 mmHg is classified as prehypertension. A person with pre-hypertensive conditions are at higher risk for progression towards hypertension. Hypertension is defined as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg. Stage 1 hypertension includes the patients having SBP between 140 and 159 mmHg or DBP ranging from 90 to 99 mmHg whereas stage 2 hypertension includes the patients with SBP $\geq$160 mmHg or DBP $\geq$100 mmHg (Liszka et al., 2005). It is evident from various scientific studies that persons with prehypertension are at particular risk of developing recognizable hypertension. Globally, increased blood pressure is estimated to cause about 12.8% of all the deaths, i.e. around 7.5 million deaths annually. In epidemiological studies, about 25% of the urban and 10% of the rural population in India were reported to have hypertension (Gupta, 2004). A positive correlation has been established between high blood pressure (HBP), coronary heart disease and ischemic and haemorrhagic stroke. Other established complications due to HBP are renal damage, heart failure, retinal haemorrhage and visual impairment. The medications suggested for the treatment of hypertension aims to bring SBP and DBP less than 140/90 mmHg which also reduces the associated cardiovascular complications. The most widely used anti-hypertensive chemical drugs are calcium channel blockers, thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and beta blockers.

Traditional medicine encompasses knowledge systems that have been established over generations based on the concepts, beliefs and practices native to diverse cultures prior to the modern medicine era. In some Asian and African countries, about 80% of the population depend on the indigenous traditional remedies for their primary health care needs which mainly involves the crude herbal-preparations (Santé, 2005). Though traditional medicines are considered safe, optimization of their appropriate doses and uses are issues worth consideration, as herbal medicines if used incorrectly may also have adverse effects. Detailed research is desirable to establish the safety and effectiveness of practices as well as plants which are used in traditional systems of medicine. Regardless of prevailing uncertainties about safety, efficacy and cost-effectiveness of complementary and alternative medicines, use of traditional plants with rational evidence of efficiency and safety will surely have social, health, and economic benefits (Pandey et al., 2013). Studies suggest that around 20,000 medicinal plants have been documented in India, out of which only 7000–7500 are in use by traditional practitioners for curing different diseases (Samy et al., 2008). Like chemical drugs, traditional or plant based medications interact and affect the functions of molecules, bio-chemicals and invading pathogens present in the human body. Among traditionally used plants, a number of Chinese medicinal plants have also been reported to be anti-hypertensive (Xiong et al., 2013). An understanding of the mechanism of action is essential to recognise the accurate actions, thus predicting and preventing its adverse events. Globally, numerous traditional medicinal plants have been investigated for their anti-hypertensive effects (Tables 1–3). However, very few scientific reports are available regarding their mode of action as summarised in Fig. 1.

Various mechanisms have been suggested for the maintenance of blood pressure in the human body. Irregularity at any of the stages may lead to changes in blood pressure resulting in hypertensive conditions. One such well known system is the renin-angiotensin-aldosterone system. Angiotensin-converting enzyme or "ACE" indirectly escalates the blood pressure and is known to cause constriction in blood vessels. It achieves this by converting angiotensin I to angiotensin II, which has an ability to constrict the blood vessels. ACE inhibitors block angiotensin-converting enzyme which results in widened and relaxed blood vessels and leads to easier blood flow through vessels, which ultimately reduces blood pressure (Atlas, 2007). Blockade of membrane embedded Ca^{2+} channels is another mechanism for reduction of hypertension. Calcium ion (Ca^{2+}) concentrations outside of cells are about 10000-fold higher than inside of cells. On receipt of certain signals, the opening of Ca^{2+} channels takes place which results in inward movement of Ca^{2+} and the associated events. Most of the calcium channel blockers, also called, calcium antagonists preferentially or exclusively block the L-type voltage-gated calcium channel (Yousef et al., 2005). Voltage-dependent calcium channels mediates excitation and contraction of skeletal, smooth and cardiac muscles and also regulates aldosterone and cortisol secretion in endocrine cells of the adrenal cortex (Felizola et al., 2014). In the heart, they mediate the conduction of the pacemaker signals. Calcium channel blockers prevent calcium from entering cells of the heart and blood vessel walls and act by one of the following mechanisms. First is through reducing the contraction of arteries by affecting the muscle cells in arterial walls which causes an increase in arterial diameter and results in lowering of blood pressure. These calcium channel blockers can also act on the cardiac muscles (myocardium) by reducing the force of contraction of the heart. By slowing down the conduction of electrical activity within the heart, they slow down the heartbeat. The calcium signals are blocked on the adrenal cortex cells which directly reduces production of aldosterone steroid hormone and results in lowering of blood pressure. Endothelin converting enzymes (ECEs) play a significant role in maintaining the blood pressure by regulating conversion of endothelins, potent vasoconstrictor peptides, into active form and vasorelaxation via nitric oxide (NO) (Yanagisawa et al., 2000). Another mechanism regulating the blood pressure is through the sympathetic and parasympathetic nervous system. Most blood vessels in the body are innervated by sympathetic adrenergic nerves, which release norepinephrine (NE) as a neurotransmitter. Some blood vessels are innervated by parasympathetic cholinergic or sympathetic cholinergic nerves, both of which releases acetylcholine as their primary neurotransmitter. NE preferentially binds α1 and α2-