The concomitant use of medicinal herbal agents with conventional medications for the treatment of a variety of medical disorders has increased considerably in recent years. This trend is likely to continue since public demand for these substances continues to grow and their market availability is constantly increasing.

Herbs that may have an effect on blood pressure are commonly used by the general population for the treatment of a variety of ailments or specifically for reducing blood pressure. Patients and doctors are often not aware of the effects these herbal agents may have on blood pressure. In addition, some of these agents may interact with drugs to cause adverse reactions. Although the prevalence of severe herbal adverse drug reactions as reported by the FDA is very low (1,2), information on the possible influence of these agents on blood pressure may prove to be important and beneficial for the general physician, pharmacist, nurse and the general patient population.

Herbal agents have been used traditionally over the millennia by most cultures around the world. The world health organization estimated recently that 40-50% of the world population is currently using herbal medicines. A survey on the use of complementary medicine in the US suggests that more than 38 million Americans used herbal medicine in 2002 (3). This data denotes a growing trend which is likely to continue (4,5).

Since many herbal medicines have been noted to have an effect on blood pressure, it is important to recognize and identify the concomitant use of these agents with conventional medications. The purpose of this article is to introduce and describe commonly used herbal medicines that may affect blood pressure.

### Effect on Blood Pressure

Approximately 100 herbs are reported in the literature to have an effect on blood pressure (6-8). Although few of these herbs were described as having the potential to increase blood pressure, the majority of the agents show an ability to decrease blood pressure. Ginseng (Panax Ginseng) is the only commonly used herb that may produce either a hypotensive or a hypertensive effect. These effects are dose dependant (9).

The pharmacological effect of herbs on blood pressure varies according to the active ingredients the herb contains. A number of herbs used in Traditional Chinese Medicine for treating high blood pressure have been studied extensively. These herbs may reduce blood pressure through a variety of known physiological mechanisms.

### The Proposed Mechanisms for Lowering Blood Pressure

- **Vasodilatation**
  - Several herbal substances have been shown to have a vasodilatory effect. Garlic for example is thought to reduce blood pressure by causing smooth muscle relaxation and vasodilation by activating production of endothelium-derived relaxation factor (EDRF, nitric oxide) (33).

- **Diuretic Effect**
  - Many commonly used herbs have been shown to have a diuretic effect. Alisma (Ze Xie – Rhizoma Alismatis), a Chinese medicinal herb commonly used to treat edema, urinary tract infections and hypertension, produces a strong diuretic effect by significantly increasing sodium excretion. The rhizome (root) increased urine volume by up to 63% (13). This herb may also induce a hypotensive response through other mechanisms such as Angiotensin-II inhibition (14).

- **Calcium Channel Blocking Effect**
  - The Chinese herb Fang Ji (Radix stephania tetrandrae) which contains the highly active component Tetrandrine, a bisbenzylisoquinoline alkaloid, reduces blood pressure by blocking inward calcium current in the benzothiazepine site of the L-type voltage-gated calcium channel (15). This herb is commonly used in Chinese medicine for the treatment of hypertension, angina pectoris and coronary diseases.
Commonly Used Herbal Medicines that Effect Blood Pressure

The following five herbal agents are commonly used by the general population for a variety of different disorders.

**Ginseng (Panax Ginseng)** - A very popular plant root grown originally in China and today also in Japan, Korea and North America. Ginseng is commonly used as an adaptogenic agent for fatigue, insomnia, anxiety, depression and immune enhancement. It is also used for increasing resistance to environmental stress and as a general enhancer of well-being. This herb is also used for improving physical and athletic performance, improving cognitive function, concentration and memory. Ginseng has a variety of active ingredients, consisting mainly of ginsenoid saponins. Ginseng is marketed either as a single herb compound or in combination with other herbs. The single herb compound is available in tablet as well as in alcoholic extracts (known as tinctures).

Experiments in dogs showed that intravenous administration of ginseng extract caused an immediate drop in blood pressure. The effect was long lasting suggesting that it might be facilitated by a Calcium channel blocking like effect (16) and interference with calcium mobilization into vascular smooth muscle cells (17). Rg1, one of the active ingredients in Ginseng can stimulate the production and release of nitric oxide (NO) from endothelial cells (18). Another ingredient, Ginsenoside Rb1 lowers blood pressure and acts as a CNS depressant (19). It also interferes with platelet aggregation and coagulation. Interestingly, Ginseng extracts exhibit a peripheral vasoconstricting effect in low doses and peripheral vasodilatation in high doses. However, in cerebral and coronary vessels it exhibits only a vasodilating effect resulting in improvement in cerebral and coronary blood flow (42). These varying effects can probably be attributed to the many different saponins that present as the active ingredients in this herb.

The potential of Ginseng to increase BP should be emphasized as this herb is not suitable for patients with hypertension and may interfere with blood pressure lowering medications. There is some evidence that Panax ginseng can inhibit the cytochrome P450 2D6 (CYP2D6) enzyme by approximately 6% (20). However, contradictory research suggests that Panax ginseng might not inhibit CYP2D6 (21). Until more is known, Panax ginseng should be used cautiously in patients taking drugs metabolized by these enzymes. Some of these drugs include amitriptyline (Elavil), clozapine (Clozaril), codeine, desipramine (Norpramin), donepezil (Aricept), fentanyl (Duragesic), flecainide (Tambocor), fluoxetine (Prozac), meperidine (Demerol), methadone (Dolophine), metoprolol (Lopressor, Toprol XL).

**Ginko (Ginko Biloba)** – The fruit and leaves of the Ginko tree are commonly used orally for dementia, including Alzheimer’s, vascular, and mixed dementia. Ginkgo leaf is also used for conditions associated with cerebral vascular insufficiency, especially in the elderly, including memory loss, headache, tinnitus, vertigo, dizziness, concentrating difficulty, mood disturbances and hearing disorders. It is also used orally for ischemic stroke. Ginko is also used for cognitive disorders secondary to depression and to improve cognitive behavior and sleep patterns in patients with depression and chronic fatigue syndrome (CFS); eye problems, including macular degeneration and glaucoma; attention deficit-hyperactivity disorder (ADHD); thrombosis; heart disease; arteriosclerosis and angina pectoris. The major active ingredients in the herb are flavonoids and glycosides. Ginko is marketed either as a single herb compound or in combination with other herbs. The single herb compound is available in tablets.

The vascular effect of Ginko extract is very well established. Considerable clinical as well as experimental evidence suggest that extracts from Ginko leaves induce vasodilation and improve vascular blood flow, particularly in the regions of the deep seated medium and small arteries (22). Overall, ginkgo leaf acts to increase cerebral and peripheral blood flow microcirculation, and reduce vascular permeability (23,24). Ginko also has a moderate blood pressure lowering effect. Evidence suggests that ginkgo leaf extract seems to increase pancreatic beta-cell function in response to glucose loading and modestly reduce blood pressure (25).

There is conflicting evidence about whether ginkgo induces or inhibits CYP3A4 (26, 27) Ginkgo does not appear to affect hepatic CYP3A4 (28). However, it is not known if ginkgo affects intestinal CYP3A4. Preliminary clinical research suggests that taking ginkgo does not significantly affect levels of donepezil, a CYP3A4 substrate (29).

Although the evidence regarding the effect of Ginkgo on cytochrome P450 is not conclusive, it is best that this herb be used cautiously in patients taking drugs metabolized by CYP3A4. This may prove particularly important with patients taking calcium channel blockers such as Nifedipine, Diltiazem and Nicardipine.

**Garlic (Allium Sativum)** - The bulb of garlic is commonly used for a variety of ailments. Garlic is used for hypertension, hyperlipidemia, coronary heart disease, age-related vascular changes and atherosclerosis, earaches, chronic fatigue syndrome (CFS), and
Menstrual disorders. Garlic is also used for cancer prevention and to treat infections. Garlic is regarded as a potent platelet aggregation inhibitor. Many of the pharmacological effects of garlic are attributed to the allicin, ajene, and other organosulfur constituents such as S-allyl-L-cysteine. Fresh garlic contains approximately 1% alliin. One milligram of alliin is converted to 0.458 mg allicin which is regarded as the major active compound in garlic. Further conversion yields ajene. The amount of allicin in garlic preparations is dependent upon the method of preparation.

Taking low doses of garlic powder orally, 300 mg per day seems to slow the age-related aortic elasticity decrease. Higher doses of 900 mg per day seem to slow development of atherosclerosis in both aortic and femoral arteries when used over a four-year period (30,31).

Evidence suggests that taking garlic orally can modestly reduce blood pressure by 2% to 7% after 4 weeks of treatment (32). Garlic is thought to reduce blood pressure by causing smooth muscle relaxation and vasodilatation by activating production of endothelial-derived relaxation factor [EDRF, nitric oxide (33)].

Clinical research suggests garlic oil can inhibit the activity of CYP2E1 by 39% (34). Garlic oil should be used cautiously in patients taking drugs metabolized by these enzymes. Some drugs metabolized by CYP2E1 include acetaminophen, chlorzoxazone (Parafon Forte), ethanol and theophylline.

There is inconsistent information about the effects of garlic on cytochrome P450 3A4 (CYP3A4) isoenzymes. Until more information is available regarding this potential interaction, use caution when considering concomitant use of garlic and other drugs metabolized by this system. Drugs that might be affected include some calcium channel blockers (diltiazem, nicardipine, verapamil).

**Dang Gui / Dong Quai (Angelicae Gigantis Radix, Chinese Angelica)** - Dang Gui is the dried root of Angelica sinesis. This herb is used extensively in Chinese medicine for a variety of gynecological disorders such as premenstrual syndrome, dysmenorrhea, irregular menstruation cycle, menstrual related bleeding disorders, menopausal symptoms and infertility. Dang Gui is also used to manage hypertension, rheumatism, ulcers, anemia, and constipation; and in the prevention and treatment of allergic attacks. The root of Dang Gui contains about 0.2-0.4% of essential oil. The major active ingredients include ferulic acid, ligusticine, angelicidce, brefeldin A, butylphthalide, nicotinic acid, and succinic acid. The herb also contains several coumarin constituents. Dang Gui is usually marketed as a single herb compound administered as powder extract in capsules. This herb is used extensively by the general population due to its potent effects on gynecological related disorders.

Dang Gui has a number of known cardiovascular and hematological effects: the essential oil caused an increase in coronary blood flow and decreased myocardial oxygen consumption; it also has mild antiarrhythmic effect (35).

Some of the coumarin constituents of this herb can act as vasodilators and antispasmodics. Osthol appears to inhibit platelet aggregation and smooth muscle contraction and cause hypotension (36). An intravenous administration of 1-4 gr/kg of the aqueous extract of the root significantly decreased arterial pressure and reduced the resistance of coronary, cerebral and femoral arteries in dogs thus significantly increasing blood flow (37). Preliminary research suggests Dang Gui might protect against ischemia-reperfusion injury (38).

Dang Gui has been reported to inhibit platelet aggregation and its concomitant use with coumadin increases the drug's anticoagulant effects, increases INR and may increase the risk of bleeding (39).

**Ma Huang (Herba Ephedra)** - The dried herbaceous stem of Ephedra sinica, Ephedra intermedia or Ephedra equisetina. Orally, ephedra is used for weight loss and enhancement of athletic performance. It is also used for allergies and allergic rhinitis; nasal congestion; and respiratory tract conditions such as bronchospasm, asthma, and bronchitis. Small doses of this herb are commonly used in traditional Chinese medicine for the treatment of asthma. All three Ephedra herbes contain the phenylproamine alkaloids l-ephedrine, d-pseudoephedrine. E. sinica contains 55-78% ephedrine and 12-23% pseudoephedrine (40).

Use of Ma Huang as a dietary supplement is prohibited in most countries including Israel. However, this herb is available for purchase in a variety of exercise performance enhancing formulas as well as weight loss formulas imported for private non commercial use.

Ephedrine, having a similar structure to epinephrine, is a well known sympathomimetic agent, acting on both α- and β-adrenergic receptors. By its β-adrenergic action, it relaxes bronchial muscles and produces the antiasthmatic action. It produces myocardial stimulation by its β1-agonist effect. Ephedrine also constricts blood vessels by its α-agonistic effect, causing an increase in blood pressure and heart rate and increasing myocardial contractility and cardiac output (40).

Use of this herb has been associated with severe adverse reactions such as myocardial infarcts and cerebral accidents (41). The ability of Ma Huang to increase BP should be emphasized as this herb may possibly interfere with blood pressure lowering medications.
Summary

Medicinal herbal agents provide a promising potential for the treatment of a variety of medical disorders. Considerable resources are currently being devoted by large pharmaceutical companies as well as by government agencies to evaluate feasibility to develop drugs from these agents. Market availability of medicinal herbs as well as public demand for these agents are constantly increasing and this trend is likely to continue. Herbs are used by the public for the treatment of a variety of medical disorders including high blood pressure. Many of these herbs may directly affect blood pressure or indirectly alter the function of blood pressure lowering medications. Improper use of herbal agents in conjunction with conventional medications may counteract or intensify the drug's effect and may produce harmful adverse reactions.

It is therefore imperative that doctors and health care practitioners acquire information from their patients regarding the use of herbal supplements. Patient intake should routinely include questions regarding the use of dietary supplements and should check for possible interactions. In addition, doctors and health care practitioners should be familiar with the commonly used herbal agents and should utilize internet and other resources that provide information regarding these substances.
In light of the high prevalence use of blood pressure lowering medications and since a substantial number of popular medicinal herbs affect blood pressure, awareness of health care practitioners and patients to this issue should further be heightened.

References