BPEX MONOGRAPH

High blood pressure is a problem for millions of Indians. Left untreated, high blood pressure can increase the chances of heart attack, blood vessel diseases, stroke, kidney disease and other complications.

Millions of Indians have high blood pressure (hypertension), but less than one third of them have achieved targeted levels of blood pressure . Out of these only 42.9% of these patients actually get their blood pressure down to acceptable levels.

Blood pressure is recorded as two numbers. Systolic pressure (the top number in a reading) denotes when the heart contracts and forces blood through the arteries; diastolic pressure (the bottom number) reflects when the heart relaxes. Normal blood pressure is 120 (systolic) over 80 (diastolic) or lower. Hypertension is defined as blood pressure averaging 140/90 or higher in at least two separate measurements.

Defined as the force the blood exerts on arteries and veins as it circulates through the body, blood pressure is controlled by a complex regulatory system involving the heart, blood vessels, brain, kidneys, and adrenal glands. It's normal for blood pressure to fluctuate often-even minute to minute. In some people, however, blood pressure remains chronically high, a condition known medically as hypertension.

REGULATION OF NORMAL BLOOD PRESSURE

- **blood pressure = cardiac output x peripheral resistance**
    - cardiac output is regulated by:
        1. cardiac factors (controlled by various neural and humoral factors)
            - heart rate
            - contractility
        2. blood volume
            - sodium
            - mineralocorticoids
            - ADH
    - peripheral resistance is regulated by:
        1. humoral factors
            - constrictors: angiotensin II; catecholamines
            - dilators: prostaglandins; kinins
        2. local factors
            - autoregulation
            - ionic (hypoxia, adenosine, pH)
        3. neural factors
            - constrictors: alpha adrenergic
            - dilators: beta adrenergic

Two forms of high blood pressure have been described.

1) Essential (or primary) hypertension
2) Secondary hypertension.

Essential hypertension is a far more common condition and accounts for 95% of hypertension. The cause of essential hypertension is multi factorial, that is, there are several factors whose combined effects produce hypertension. In secondary hypertension, which accounts for 5% of hypertension, the high blood pressure is secondary to (caused by) a specific abnormality in one of the organs or systems of the body.

Most people who have high blood pressure do not know they have it because they generally experience no symptoms at all. Occasionally, some individuals may experience a mild headache when their blood pressure is high. Serious cases of hypertension, which happen infrequently, may produce the following symptoms:

- Severe headache
- Confusion
- Nausea
- Visual disturbances
- Seizure

Pathology

No early pathologic changes occur in primary hypertension. Ultimately, generalized arteriolar sclerosis develops; it is particularly apparent in the kidney (nephrosclerosis) and is characterized by medial hypertrophy and hyalinization. Nephrosclerosis is the hallmark of primary hypertension. Left ventricular hypertrophy and, eventually, dilation develop gradually. Coronary, cerebral, aortic, renal, and peripheral atherosclerosis are more common and more severe in hypertensives because hypertension accelerates atherogenesis. Hypertension is a more important risk factor for stroke than for atherosclerotic heart disease. Tiny Charcot-Bouchard aneurysms, frequently found in perforating arteries (especially in the basal ganglia) of hypertensives, may be the source of intracerebral hemorrhage.

The pathological changes in blood vessels observed in primary (essential hypertension) are similar to those seen in secondary hypertension due to renal disease or other causes. In benign hypertension, the major changes are in the small arteries and arterioles especially in the kidney. Interlobular arteries exhibit intimal thickening and duplication of the elastic lamina (elastosis) and there is hyaline change in the media of many arterioles. In some respects these changes are an accentuation of vessel ageing. Malignant hypertension usually presents in a younger age group (35--50 years) and is characterized pathologically by fibrous endarteritis in the interlobular arteries of the kidney and fibrinoid necrosis in the walls of a proportion of the efferent glomerular arterioles. Similar vessel changes are seen in other organs but many of the pathological changes in the heart and brain of patients with benign hypertension are related to the accentuation of arterosclerosis. There is an increased mortality from cardiac failure, myocardial infarction, cerebral haemorrhage and subarachnoid haemorrhage due to ruptured berry aneurysms in patients with benign hypertension. Although there is ischaemic damage to the kidneys in benign hypertension, death from renal failure is uncommon. Severe ischaemic damage to renal glomeruli and renal failure does, however, occur in malignant hypertension.

The goal in treating hypertension is to reduce the risk of serious complications, including heart disease and stroke. While the optimum blood pressure is 120/80 mm Hg, even partial reduction in blood pressure is beneficial. Prescription medications are often needed to treat hypertension, but lifestyle modifications, including diet, exercise, and relaxation, are necessary with or without medications. In fact, a National Institute of Health (NIH) statement issued in 1996 asserts that behavioral and relaxation therapies must be integrated into conventional medical treatment of high blood pressure. Examples of relaxation techniques include biofeedback, massage and meditation. Often, in the early stages of hypertension when blood pressure elevation is mild, the doctor will recommend lifestyle modifications alone for a period of 6 to 12 months. After this time, if blood pressure is still high, medication will likely be prescribed.

Lifestyle modifications: Extra rest, prolonged vacations, moderate weight reduction, and dietary Na restriction are not as effective as antihypertensive drug therapy. Patients with uncomplicated hypertension need not restrict their activities as long as their BP is controlled. Dietary restrictions can help control diabetes mellitus, obesity, and blood lipid abnormalities. In stage 1 hypertension, weight reduction to ideal levels, modest dietary Na restriction to < 2 g/day, and alcohol consumption to < 1 oz/day may make drug therapy unnecessary. Prudent exercise should be encouraged. Smoking should be unambiguously discouraged.

The following formulations of herbs is known to control hypertension in the most modest way.

Terminalia arjuna	200mg
Boerhaavia diffusa	100mg
Ocimum sanctum	100mg
Coleus forkshill	100mg
Jatamansi	100mg

Coleus forskohlii

Coleus forskohlii, is a member of the mint family (Lamiaceae). As part of a long-standing tradition in India, C. forskohlii roots have been used as a marinated food, or pickle, that is commonly eaten as part of a vegetarian meal. Upon closer investigation into the plant's pharmacological properties, it was revealed that C. forskohlii roots contain forskolin, a compound that belongs to the chemical class of diterpenes.

Forskolin (7b-acetoxy-8,13-epoxy-1a,6b,9a-trihydroxylabd-14-en-11-one), a diterpene compound, is a major biologically active component of Coleus forskohlii roots. In nature, forskolin has only been found in the roots of the Coleus forskohlii plant. Minor diterpenoids, deacetylforskolin, 9-deoxyforskolin, 1,9-deoxyforskolin, 1,9-dideoxy-7-deacetylforskolin, and four other diterpenoids, have also been reported to be present in the roots of Coleus forskohlii.

Forskolin has mutifaceted pharmacological effects that have been linked to its role as an activator of adenylate cyclase.3 Adenylate cyclase is the enzyme involved in the production of cyclic adenosine monophosphate (cAMP), a significant biochemical agent involved in essential metabolic processes. Cyclic AMP is called the "second messenger" because it facilitates the action of "primary messengers", various hormonal and bioactive substances in the body. Based on its pharmacological actions, forskolin appears to be well indicated in conditions, such as eczema (atopic dermatitis), asthma, psoriasis, cardiovascular disorders, and hypertension, where decreased intracellular cAMP levels is believed to be a major factor in the development of the disease process.

The basic mechanism of action of forskolin is the activation of an enzyme, adenylate cyclase, which increases cyclic adenosine monophosphate (cAMP) in cells. Cyclic AMP is perhaps the most important cell-regulating compound. Once formed it activates many other enzymes involved in diverse cellular functions. Under normal situations cAMP is formed when a stimulatory hormone (e.g., epinephrine) binds to a receptor site on the cell membrane and stimulates the activation of adenylate cyclase. This enzyme is incorporated into all cellular membranes and only the specificity of the receptor determines which hormone will activate it in a particular cell. Forskolin appears to bypass this need for direct hormonal activation of adenylate cyclase via transmembrane activation. As a result of this activation of adenylate cyclase intracellular cAMP levels rise. The physiological and biochemical effects of a raised intracellular cAMP level include:

inhibition of platelet activation and degranulation;

inhibition of mast cell degranulation and histamine release;

increased force of contraction of heart muscle;

relaxation of the arteries and other smooth muscles;

increased insulin secretion;

increased thyroid function;

and increased lipolysis.

Recent studies have found forskolin to possess additional mechanisms of action independent of its ability to directly stimulate adenylate cyclase and cAMP dependent physiological responses. Specifically forskolin has been shown to inhibit a number of membrane transport proteins and channel proteins through a mechanism that does not involve the production of cAMP. The result is again a transmembrane signaling that results in activation of other cellular enzymes. Research is underway in the attempt to determine the exact receptors to which the forskolin is binding.

As a therapeutic intervention in congestive heart failure, forskolin has been shown to activate the enzyme adenylate cyclase, which increases production of cyclic adenosine monophosphate (cAMP) in heart muscle cells (cardiac muscle). Epinephrine has a similar effect on increasing cAMP. Increased levels of cAMP, in turn, increase the ability of the heart muscle to produce ATP, the energy required for heart-muscle contraction and its optimal force with each beat (increased stroke volume). Forskolin also relaxes the artery wall, decreasing blood pressure and preload stress on the heart muscle. All of these effects appear to be mediated via increased cAMP synthesis, which acts as a secondary messenger on various cellular processes that manifest the stated outcomes.

Hypertension. As mentioned, forskolin relaxes blood vessel smooth muscles via increased cAMP synthesis, helping to reduce high blood pressure by reducing resistance to blood flow.

During the eight week trial, the mean values for body weight and fat content significantly decreased, whereas lean body mass significantly increased compared to baseline values The regimen did not adversely affect the systolic/diastolic blood pressure nor the pulse rate. In fact, a trend towards lower systolic/diastolic pressure was observed during the study

Terminalia Arjuna

It has main constituents like tannins, triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin, arjunglycosides), flavonoids (arjunone, arjunolone, luteolin), gallic acid, ellagic acid, oligomeric proanthocyanidins (OPCs), phytosterols, calcium, magnesium, zinc, and copper.

Remedies For: Cardiac stimulant, Rejuvenative, Astringent, Hemostatic.

The hot water infusion of Terminalia arjuna possesses a mild diuretic and fairly potent cardiac stimulant and cardio tonic activity. The total extract of Terminalia arjuna bark stimulates the force of contraction with a marginal increase in rate of heartbeat. The amplitude of contraction increases with an increase in the dose of the plant bark up to a certain extent. Intravenous administration of extract of Terminalia arjuna bark induces a dose dependent decrease in blood pressure and heart rate. The extract also inhibits carotid occlusion response, without affecting the pressor response. Hypotension and bradycardia were also observed following the injection of the extract into the lateral cerebral ventricles and vertebral artery. This result suggests that the hypotensive bradycardiac effects of Terminalia arjuna are mainly of central origin.

In one of the studies Terminalia arjuna exhibited increase in the coronary flow of the blood in Coronary heart diseased patients.

Terminalia arjuna is known to inhibit cholesterol biosynthesis and potentiate the activity of lipolytic enzymes to early clearance of lipids from the circulation in triton-induced hyperlipaemia.

Hyperlipaemia causes inhibition of hepatic lipolytic activity and specific binding of I-125 –LDL in membrane, Terminalia arjuna is known to restore the enzyme activity and receptor mediated catabolism of LDL. Terminalia arjuna administered in hyperlipamic subjects inhibited the over all hepatic lipid biosynthesis as evidenced by the decreased incorporation of sodium acetate in total sterol, cholesterol-digitonoid and free fatty acid fractions of liver lipids. Terminalia arjuna enhances the synthesis of LDL apo proteins as well as receptor protein and inhibits the oxidative modification of LDL to accelerate the turn over of LDL cholesterol in the liver. Terminalia arjuna also inhibits the HMG-CoA reductase, the rate limiting enzyme in the hepatic cholesterol biosynthesis. The abnormalities in the synthesis and the catabolism in the body lipids are closely related to plasma lecithin, cholesterol acyltransferace (LCAT) deficiency and hepatic dysfunction in hyperlipaemia. LCAT, a key enzyme involved in body lipid metabolism, is solely synthesized in liver and therefore hepatoprotective action of Terminalia arjuna may contribute to the improved liver function, reactivation of LCAT and regulations of lipids. Terminalia arjuna enhances the fecal excretion of cholic acid and deoxycholic acid. This indicates that Terminalia arjuna interferes with the absorption of the dietary cholesterol in small intestine.

Thus the stimulation of plasma LCAT, hepatic lipase, receptor mediated catabolism of LDL and increased faecal bile acid excretion as well as suppression of hepatic cholesterol bio synthesis by Terminalia arjuna are the mechanism responsible for a significant lowering of beta lipoproteins –lipids and the recovery of HDL components in hyperlipaemic animals.

Clinical Applications

Angina Pectoris

An open study of Terminalia use in stable and unstable angina demonstrated a 50-percent reduction of angina in the stable angina group after three months ($p < 0.01$). A significant reduction was also found in systolic blood pressure in these patients ($p < 0.05$). During treadmill testing, both the onset of angina and the appearance of ST-T changes on ECG were significantly delayed in the stable angina group ($p < 0.001$), indicating an improvement in exercise tolerance. The unstable angina group did not experience significant reductions in angina or systolic blood pressure. Both groups showed improvements in left ventricular ejection fraction. Evaluation of overall clinical condition, treadmill results, and ejection fraction showed

improvement in 66 percent of stable angina patients and 20 percent of unstable angina patients after three months.

Congestive Heart Failure

A double-blind, placebo-controlled, two-phase trial of Terminalia extract treatment in twelve patients with severe refractory heart failure (NYHA Class IV) was conducted. Either 500 mg Terminalia bark extract or placebo was given every 8 hours for two weeks, in addition to the patients' current Terminalia arjuna pharmaceutical medications (digoxin, diuretics, angiotensin-converting-enzyme inhibitors, vasodilators, and potassium supplementation). All patients experienced dyspnea at rest or after minimal activity at the start of the trial. Dyspnea, fatigue, edema, and walking tolerance all improved while patients were on Terminalia therapy. Treatment with Terminalia was also associated with significant improvements in stroke volume and left ventricular ejection fraction, as well as decreases in end-diastolic and end-systolic left ventricular volumes compared to placebo. In the second phase of the study, patients from phase I continued on Terminalia extract for approximately two years. Improvements were noted in the ensuing two to three months, and were maintained through the balance of the study. After four months' treatment, nine patients had improved to NYHA Class II and three improved to Class III.

Cardiomyopathy/Post-Myocardial Infarction

A study was conducted on 10 post-myocardial-infarction patients and two ischemic cardiomyopathy patients, utilizing 500 mg bark extract every eight hours for three months, along with conventional treatment. Significant reductions in angina, left ventricular ejection fraction, and left ventricular mass were noted in the Terminalia group, whereas the control group taking only conventional drugs had decreased angina only. The two patients with cardiomyopathy improved from NYHA Class III to Class I during the study.

Hyperlipidemia

Animal studies suggest Terminalia might reduce blood lipids. Rabbits made hyperlipidemic by feeding them an atherogenic diet were given an oral Terminalia extract. Animals given Terminalia had a significant, dose-related decrease in total- and LDL-cholesterol, compared to placebo ($p < 0.01$). However, the amounts used (100 mg/kg and 500 mg/kg body weight) were very large, and it remains to be seen if these significant changes will be seen in humans taking relatively smaller oral doses. In a similar study of rats fed cholesterol (25 mg/kg body weight) alone or along with Terminalia bark powder (100 mg/kg) for 30 days, Terminalia feeding caused a smaller increase in blood lipids and an increase in HDL cholesterol compared to the cholesterol-only group. The researchers felt inhibition of hepatic cholesterol biosynthesis, increased fecal bile acid excretion, and stimulation of receptormediated catabolism of LDL cholesterol caused Terminalia's lipid-lowering effects.

The hypotension produced by 6 mg/kg body weight dose of the extract was not blocked by atropine which could block the response of selected dose of acetylcholine indicating that the muscarinic mechanism was not involved. Studies with mepyramine maleate indicate that histaminergic mechanism was also not involved in the hypotension produced by the extract. Studies with propranolol which blocked the hypotensive response of the extract indicated that it may contain compounds having adrenergic ß-receptor agonist action. Even though propranolol is a non-specific ß-blocker, it is clear that the compounds present in the extract might be adrenergic $ß_2$-agonists, since adrenergic $ß_2$-receptor stimulation produces hypotension.

B.diffusa

B.diffusa is commonly used diuretic in Ayurvedic system of medicine.B.diffusa when administered to the patient with nephrotic syndrome showed marked improvement in the level of Hb% which may be due to the release of erythropoietin from the kidney. It also exerts a significant reduction in serum creatinine level and marginal

decrease in blood urea levels with prolongs medication. This effect is attributed towards increased diuresis leading to increased excretion of nitrogenous substance in the urine. Prolong use of B.diffusa shows progressive changes in serum sodium and potassium. A rise in serum proteins is also seen after the prolong use of B. diffusa. As per the research workers the plant may have some effect on protein metabolism through its role on liver.

O.sanctum

Crude aqueous extract of O.sanctum leaves showed transient hypotensive effect in anaesthetized dogs and cats and a negative inotropic and chronotropic effects on rabbit heart. The extract also inhibits the smooth muscles spasm induced acetylcholine and histamine.